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American Journal of Diseases of Children

VOULME 74 SEPTEMBER 1947 NUMBER 3

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PREVALENCE OF DENTAL CARIES IN MALNOURISHED CHILDREN

A Clinical Study

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AND

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IN A REVIEW of the basic considerations of dental caries, Rosebury distinguished between two varieties of the disease.[1] The first and distinctly more common type attacks the pits and fissures of the crown or the neighborhood of points of contact of approximating teeth. This type predominates in the teeth of children and young persons. The second and less common variety is found principally in the teeth of adults and appears in the gingival area of the crown or in exposed roots. Because the first variety is by far the more prevalent, dental caries is regarded as predominantly a disease of children and young persons, an observation reported many years ago by G. V. Black.[2] The highest incidence of caries is noted usually during the period of eruption of the teeth. This is particularly true during the transition from deciduous to permanent dentition, as both dentitions are affected during this time.

Statistical data obtained by investigators in the fields of children's dentistry and public health lend support to the conclusions of Rosebury. Klein, Palmer and Knutson,[3] in a study on 4,416 grade school children

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These studies were supported by grants from the Martha Leland Sherwin Memorial Fund and the Abbott Laboratories.

1. Rosebury, T.: The Problem of Dental Caries, cited by Gordon, S. M.: Dental Science and Dental Art, Philadelphia, Lea & Febiger, 1938, p. 273.

2. Black, A. D.: G. V. Black's Work on Operative Dentistry, ed. 7, Chicago, Medico-Dental Publishing Company, 1936, p. 321.

3. Klein, H.; Palmer, C. E., and Knutson, J. W.: Studies on Dental Caries: I. Dental Status and Dental Needs of Elementary School Children, Pub. Health Rep. **53**:751 (May 13) 1938.

from 6 through 15 years of age in Hagerstown, Md., found that 3,156, or 71.5 per cent, showed a history of caries in one or more permanent teeth. Arnold and McClure [4] examined 127 seventh grade children in Arlington County, Va., between the ages of 11 and 15, and reported that 96.1 per cent of all children examined showed evidence of dental caries. Day and Sedwick,[5] working in Rochester, N. Y., found the incidence of caries of 433 children to be 99.8 per cent. Only 1 of the 433 children was completely free of the disease.

Klein and Palmer [6] reported also that the rate of caries attack for all groups was of the order of 1.8 DMF [7] tooth surfaces per child per year of school attendance, or 0.7 permanent tooth per child per year. McQuarrie, Midgely, Swanson, Wilson and Brekhus [8] gave a slightly higher figure for the rate of caries attack (9/12 to 11/12 tooth per child per year) in their review of the literature dealing with the occurrence and treatment of dental caries among school children from the ages of 6 to 18 years in the United States. Since White [9] reported that an average of 1.4 carious surfaces per mouth is overlooked when roentgenograms are not used in conjunction with examination with a mouth mirror and explorer tine, it appears that the values presented by Klein and Palmer and McQuarrie and associates are somewhat conservative and that the actual yearly rate of increase of dental caries in children might be closer to 2.0 DMF tooth surfaces per child per year.

The extent to which rates of attack of dental caries in children can be influenced by nutritional procedures occupies a significant part of the dental literature. A. D. Black [2] stated that caries is often increased in cases of malnutrition, and Boyd and Drain [10] and Boyd, Drain and Nelson [11] reported that an improvement in the nutritional adequacy of

4. Arnold, F. A., Jr., and McClure, F. J.: A Study of the Relationship of Oral Lactobacillus Acidophilus and Saliva Chemistry to Dental Caries, Pub. Health Rep. **56**:1495 (July 25) 1941.

5. Day, C. D. M., and Sedwick, H. J.: Studies on the Incidence of Dental Caries, Dent. Cosmos **77**:442 (May) 1935.

6. Klein, H., and Palmer, C. E.: The Disparity Between Dental Need and Dental Care in School Children of Hagerstown, Md., and Environs, J. Am. Dent. A. **28**: 1489 (Sept.) 1941.

7. D indicates number of decayed tooth surfaces; M, number of missing teeth extracted because of caries or complications resulting from caries (each missing tooth is equal to five tooth surfaces [6]); F, number of tooth surfaces restored.

8. McQuarrie, I.; Midgely, A. L.; Swanson, E. W.; Wilson, D. W., and Brekhus, P. J.: A Study of the Occurrence and Treatment of Dental Caries Among School Children Aged 6-18 in the United States, J. Am. Dent. A. **31**:322 (March) 1944.

9. White, D. P.: Preliminary Bite-Wing Roentgenographic Examination of Naval Aviation Cadets, U. S. Nav. M. Bull. **43**:901 (Nov.) 1944.

10. Boyd, J. D., and Drain, C. L.: Arrest of Dental Caries in Childhood, J. A. M. A. **90**:1867 (June 9) 1928.

11. Boyd, J. D.; Drain, C. L., and Nelson, M. V.: Dietary Control of Dental Caries, Am. J. Dis. Child. **38**:721 (Oct.) 1929.

the diet results in a reduction of the incidence of dental caries in children. Bowes [12] attributed a reduction in prevalence of caries in children to a well regulated routine, a diet that is really adequate, few sweets, no snacks between meals, good hygiene and continuous dental supervision. However, the exact role of diet in prevention of caries is still the subject of much controversy. In 1945 Schour and Massler [13] reviewed the literature and concluded that "present evidence has not established a specific nutritional basis for caries or for periodontal disease."

Mann, Dreizen, Spies and Hunt [14] compared the incidence of dental caries in well nourished and malnourished persons in the nutrition clinic at the Hillman Hospital, Birmingham, Ala. Their results substantiated earlier observations [15] that in persons with vitamin B complex and associated deficiencies the incidence of dental caries is lower than it is in well nourished persons. In view of these findings and the fact that dental caries is predominantly a disease of childhood, it seemed of importance to study the immunity and susceptibility to dental decay in malnourished and in well nourished children in the same geographic area and, at the same time, to determine the yearly rate of increase in the number of tooth surfaces affected by decay in children whose diet had always been inadequate and the rate for children whose diet had always been adequate.

MATERIAL AND METHODS

Selection of Patients.—Seventy-two children with clinical evidence of nutritional deficiency diseases were selected for this investigation. These children were from rural areas in north central Alabama, a region in which nutritional deficiency diseases are endemic. Each child selected had been examined periodically at the Nutrition Clinic for several years prior to the time this study was undertaken. In many instances the parents and older siblings also had been under observation at the Clinic for the last decade and at various times had had clinical evidence of one or more of the nutritional deficiency diseases.

Records showed that the diets of the mothers of these children were usually inadequate during pregnancy and lactation and that the supply of breast milk was scanty. In spite of the scarcity of milk, most of the children were breast fed, some

12. Bowes, A. deP.: Dentistry and Diet, J. Am. Dent. A. **30**:1360 (Sept.) 1943.

13. Schour, I., and Massler, M.: The Effects of Dietary Deficiencies upon the Oral Structures, J. Am. Dent. A. **32**:1022 (Aug.) 1945.

14. Mann, A. W.; Dreizen, S.; Spies, T. D., and Hunt, F. M.: A Comparison of Dental Caries Activity in Malnourished and Well Nourished Patients, J. Am. Dent. A. **34**:244 (Feb. 15) 1947.

15. Mann, A. W.; Spies, T. D., and Springer, M.: The Oral Manifestations of Vitamin B Complex Deficiencies, J. Dent. Research **20**:269 (June) 1941. Sandwith, F. H.: The Medical Diseases in Egypt, London, H. Kimpton, 1905, p. 137. Corkhill, N. L.: Pellagra in Sudanese Millet Eaters, Lancet **1**:1387 (June 30) 1934. Roberts, S. R.: Pellagra, St. Louis, C. V. Mosby Company, 1915, p. 109.

of them for as long as two or three years.[16] Because of the scarcity of the mother's milk supply, the children were given additional foods, such as corn bread, biscuits, syrup and grits, at an early age. Few of them had received supplements of orange juice or cod liver oil. As the children grew older, they usually had poor appetites and ate irregularly. A great number of them preferred high carbohydrate foods to all others.[17]

For the purpose of confining the comparison of the incidence of dental caries to the same geographic locale, an additional 25 well nourished children from this region were selected. The mothers of the children in this group had all been under the care of physicians during the prenatal period, in striking contrast to the almost total lack of professional prenatal care for the mothers of the malnourished children.

The 97 children were divided into three groups. Group 1 consisted of 47 malnourished children; group 2 consisted of 25 malnourished children who, beginning in March 1945, received a supplement of 1 quart (1,000 cc.) of milk per

TABLE 1.—*Age Distribution of Seventy-Two Malnourished and Twenty-Five Well Nourished Children*

Age in Years at End of Experimental Period	Group 1*	Group 2†	Group 3‡	Total
5	2	0	0	2
6	3	2	2	7
7	1	1	3	5
8	4	3	2	9
9	6	2	2	10
10	3	2	3	8
11	5	6	2	13
12	4	2	6	12
13	7	3	2	12
14	3	2	2	7
15	6	0	1	7
16	2	2	0	4
17	1	0	0	1
Total	47	25	25	97

* Group 1 consisted of 47 nutritionally deficient children.
† Group 2 consisted of 25 nutritionally deficient children receiving milk supplement.
‡ Group 3 consisted of 25 control children free of symptoms of nutritional deficiency disease (children in adequate nutritional state).

day, six days per week, a practice which is still maintained,[18] and group 3 consisted of 25 well nourished children on an adequate diet who were free from evidence and/or history of nutritional deficiency disease. Group 3, therefore, constituted the control group.

The 47 children (20 boys and 27 girls) of group 1 ranged in age from 5 to 17 years; the 25 children (11 boys and 14 girls) of group 2, from 6 to 16 years, and the 25 control children (10 boys and 15 girls) of group 3, from 6 to 15 years (table 1). All the children were white.

16. Spies, T. D.; Bean, W. B.; Vilter, R. W., and Huff, N. E.: Endemic Riboflavin Deficiencies in Infants and Children, Am. J. M. Sc. **200**:697 (Nov.) 1940.

17. Spies, T. D.; Ewing, G. D., and Mann, A. W.: Effect of Synthetic Niacin Amide, Synthetic Thiamine, and Synthetic Riboflavin on Infants and Young Children with Deficiency Diseases, Arch. Pediat. **61**:517 (Oct.) 1944.

18. The milk supplement was given for the purpose of studying growth changes, as part of another investigation now under way at the Nutrition Clinic.

Methods of Study.—The nutritional status of the patients was determined by medical examinations for signs and symptoms of deficiency states. These examinations were made four times during each calendar year by the physicians and dentists on the staff of the Nutrition Clinic. Dietary histories were obtained in each case. Evaluations of the nutritive value of the diets were made by Mrs. Elizabeth Slater Seay. The dental examinations were made with a mouth mirror and an explorer tine and were supplemented in every instance by "bitewing" or full mouth roentgenograms. The children were examined by staff dentists in August 1945 and reexamined one year later, in August and September 1946.

OBSERVATIONS

The clinical evidences of nutritional deficiency disease are summarized in table 2. Of the children of group 1, 44 had clinical evidence of riboflavin deficiency; 2, of nicotinic acid deficiency; 4, of thiamine deficiency; 4, of ascorbic acid deficiency, and 9, of vitamin A deficiency. In group 2, 20 of the children had signs and symptoms of riboflavin deficiency; 2, of thiamine deficiency; 12, of ascorbic acid deficiency, and 5, of vitamin A deficiency. Thirty of the children in groups 1 and 2 showed evidence of multiple deficiency disease, which is common among malnourished persons.[19] No evidence of rickets was seen in any of these children. (The amount of sunlight in this section of the country is high, and nearly all the children in this series were exposed to it early in life.[20])

TABLE 2.—*Distribution of Clinical Evidence of Nutritional Deficiency Diseases in Seventy-Two Malnourished and Twenty-Five Well Nourished Children*

Deficiency	Group 1	Group 2	Group 3
Riboflavin	44	20	0
Nicotinic acid	2	0	0
Thiamine	4	2	0
Ascorbic acid	4	12	0
Vitamin A	9	5	0
Total	63*	39*	0

* Thirty of the children in groups 1 and 2 showed evidence of multiple deficiency disease.

The results of the dietary evaluations are presented in the chart. None of the children in group 1 or group 2 was on a diet which was regarded as adequate in all respects. The diets of the children receiving the milk supplement, however, were adequate in calcium, phosphorus,

19. Spies, T. D.; Bean, W. B., and Ashe, W. F.: Recent Advances in the Treatment of Pellagra and Associated Deficiencies, Ann. Int. Med. **12**: 1830 (May) 1939.

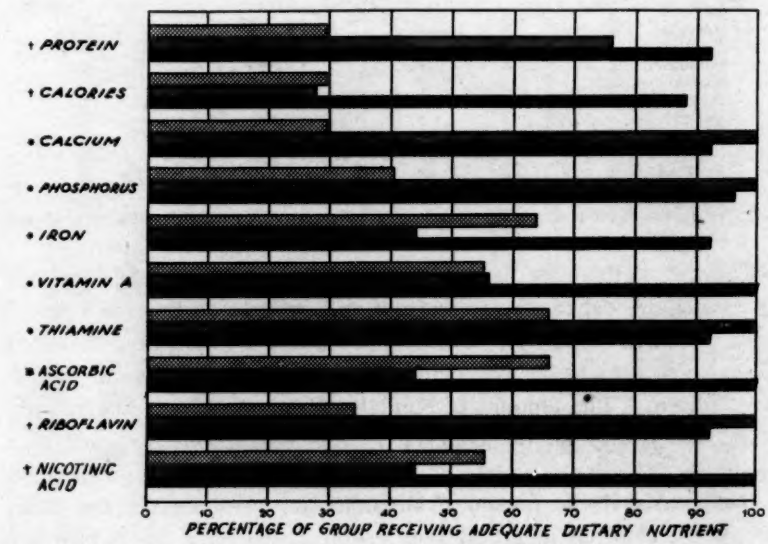
20. According to the Birmingham Weather Bureau, in a personal communication, Jefferson County, of which Birmingham is the county seat, has 62 to 63 per cent of sunshine per year, where 100 per cent represents continual sunshine from sunrise to sunset for all 365 days of the year.

thiamine and riboflavin. The inadequacies listed in group 3 were all borderline and were noted in the histories of 3 of the children.

The distribution of carbohydrate in the dietaries of the children investigated is listed in table 3. It is of especial interest to note that the average total carbohydrate intake per day per child in terms of grams was 248 for group 1, 253 for group 2 and 291 for group 3. These values constituted 54, 55 and 49 per cent, respectively, of the total caloric intake. The average refined carbohydrate [21] intake per day per

TABLE 3.—*Daily Carbohydrate Intake of Seventy-Two Malnourished and Twenty-Five Well Nourished Children*

Group	Total Carbohydrate Intake		Refined Carbohydrate Intake	
	Average per Day, Gm.	Average per Cent of Total Caloric Intake per Day	Average per Day, Gm.	Average per Cent of Total Caloric Intake per Day
1.....	248	54	52	12
2.....	253	55	48	11
3.....	291	49	67	11



Comparison of the percentages for each group of children whose diet was adequate in the nutrients evaluated.

The rectangles in cross hatchure represent the malnourished children not receiving a milk supplement (group 1); the rectangles with single hatchure, the malnourished children receiving a milk supplement (group 2), and the black rectangles, the well nourished, control children (group 3).

The nutrients marked with the asterisk met the minimum dietary allowance recommended by the Food and Drug Administration, Federal Security Agency; the nutrients marked with the dagger were adequate according to the standards recommended by the Council on Foods and Nutrition, the National Research Council.

21. Desserts, sugar, syrup, soft drinks and candy.

child in terms of grams was 52 for group 1, 48 for group 2 and 67 for group 3. These values constituted 12, 11 and 11 per cent, respectively, of the total caloric intake.

Table 4 shows the results of the dental examinations. The average value for the DMF (decayed-missing-restored) tooth surfaces for the children of group 1 was 4.52 at the start of the study and 4.82 at the completion of the period of investigation. The resulting increase was 0.95 DMF tooth surface per child per year. The children in group 2 averaged 2.80 DMF tooth surfaces at the beginning of the study and 3.76 DMF surfaces at the end of the experimental period. This group, therefore, showed an increase of 0.96 DMF tooth surface per child per year. The children of group 3, the control group, had an average of 7.34 DMF tooth surfaces at the beginning of the study and 10.32 DMF surfaces at the close. The increase for this group was 2.38 DMF tooth surfaces per child per year. The incidence of dental caries in the two

TABLE 4.—*Comparison of DMF Surfaces in Seventy-Two Malnourished and Twenty-Five Well Nourished Children*

Tooth Surfaces	Group 1			Group 2			Group 3		
	Average No.		Average Increase	Average No.		Average Increase	Average No.		Average Increase
	Examination 1	Examination 2	per Child/Yr.	Examination 1	Examination 2	per Child/Yr.	Examination 1	Examination 2	per Child/Yr.
Decayed (D)....	3.45	3.53	0.79	2.28	3.04	0.92	2.58	4.00	1.42
Missing (M)*....	0.96	1.18	0.21	0.20	0.40	0.20	0.40	0.60	0.20
Restored (F)....	0.11	0.11	0.00	0.32	0.32	0.00	4.36	5.72	0.76
Total.....	4.52	4.82	0.95	2.80	3.76	0.96	7.34	10.32	2.38

* Each missing tooth is regarded as equivalent to five surfaces.

groups of malnourished children was only 44.46 per cent of that observed for the control group. Seven (15 per cent) of the children in group 1 were completely free of caries; 3 (12 per cent) of the children in group 2 showed no evidence of caries, while 2 (8 per cent) of the children in group 3 were free from caries.

Examination of the data pertinent to the deciduous dentition in the three groups showed carious involvement of the deciduous teeth as follows: group 1, 34 per cent; group 2, 32 per cent, and group 3, 35 per cent.

COMMENT

The difference in the incidence of dental caries for well nourished children and that for malnourished children is difficult to explain on the basis of present knowledge of dental caries. Two distinct schools of thought have developed through the years, in an attempt to explain differences in immunity or susceptibility to dental caries. Howe,[22]

22. Howe, P. R.: Dental Caries, Dent. Cosmos **62**:921 (Aug.) 1920.

Mellanby [23] and Boyd and Drain,[10] among others, expressed the belief that the most important single factor in prevention of dental caries is the resistance of the tooth itself, while in the opinion of Bunting,[24] Hawkins and associates,[25] Hanke,[26] Fosdick [27] and Stephan [28] and their followers the local environment of the tooth is all-important in the process of dental decay.

Neither theory completely explains the results obtained in this study that children fed an inadequate diet since infancy have an incidence of caries only 44.46 per cent as high as that of a corresponding group of children fed an adequate diet during the period of growth and development of their permanent teeth. Furthermore, the percentages of deciduous teeth involved by dental caries are comparatively equal for the two groups despite the fact that the mothers of the malnourished children had almost complete lack of prenatal care, whereas the mothers of the control children were all under the care of physicians during the prenatal period.

The factor of local environment is inadequate to explain the difference in this instance, as the two groups of children ingested about the same amount of refined carbohydrates. The malnourished children rarely, if ever, visited a dentist, as was evidenced by the accumulations of detritus and stain in their mouths and the almost total absence of restorative work, while the mouths of the children in the control group were in general free from deposits and stain and contained an average of 5.72 restorations per mouth per child. The fluorine content of the local water supply was far below the 1 part per million regarded as the effective concentration necessary for control of caries.[29] Deficiencies of nicotinic acid and thiamine, both necessary in the enzymatic reactions of the carbohydrate degradation process, might offer a partial explanation,

23. Mellanby, M.: Experimental Study of the Influence of Diet on Tooth Structure, Dent. Rec. **39**: 22 (Jan.) 1919.

24. Bunting, R. W.: A Review of Recent Researches on Dental Caries, J. Am. Dent. A. **28**:785 (May) 1931.

25. Hawkins, H. F.; Hendricks, W. W., and Hills, N. R.: Cause and Prevention of Dental Caries as Indicated by a Survey, J. Am. Dent. A. **15**:354 (Feb.) 1928.

26. Hanke, M. T.: Relation of Diet to General Health and Particularly to Inflammation of Oral Tissues and Dental Caries, J. Am. Dent. A. **17**: 957 (June) 1930.

27. Fosdick, L. S.: The Present Status of the Dental Caries Problem at Northwestern, Bull. Northwestern Univ. (no. 20) **43**:4 (March 8) 1943.

28. Stephan, R. M.: Intra-Oral Hydrogen-Ion Concentration Associated with Dental Caries Activity, J. Dent. Research **23**:257 (Aug.) 1944.

29. Dean, H. T.; Jay, P.; Arnold, F. A., and Elvove, E.: Domestic Water and Dental Caries: II. A Study of 2,832 White Children Aged 12-14 Years of Eight Suburban Chicago Communities, Including Lactobacillus Acidophilus Studies of 1,761 Children, Pub. Health Rep. **56**:761 (April) 1941.

although the work of Kniesner, Mann and Spies [30] indicates that the daily food intake of persons showing vitamin B complex and associated deficiencies is sufficient to meet the growth requirements of the Lactobacillus acidophilus. An interesting point of difference was reported in an earlier investigation by Dreizen, Mann, Cline and Spies,[31] when they noted that malnourished patients relatively free from dental caries had a buffer capacity of the saliva 55.7 per cent greater than that of well nourished patients with moderate or rampant caries.

It would appear that many factors which may cause or predispose to dental decay are yet to be determined before it will be possible to account for all the inconsistencies of findings in connection with dental caries.

SUMMARY AND CONCLUSIONS

The incidence of dental caries was determined in 72 children with signs and symptoms of malnutrition, as well as in a control group of 25 well nourished children from the same geographic area. Twenty-five of the malnourished children had been on a supplement of 1 quart (1,000 cc.) of milk per day for eighteen months. The following observations were made:

1. There was no apparent difference in the incidence of dental caries in the deciduous dentition in the malnourished and in the adequately nourished children.

2. There was no significant difference in the incidence of dental decay in malnourished children receiving a supplement of 1 quart of milk per day for a period of eighteen months and in those not receiving the milk supplement.

3. The malnourished children showed an average yearly increase of 0.95 DMF (decayed-missing-restored) tooth surface per child, as compared with a national average of approximately 2.0 DMF tooth surfaces per child per year. The control children averaged an increase of 2.38 DMF surfaces per child per year.

4. Regardless of the milk supplement, the malnourished children had an incidence of caries only 44.46 per cent of that for the control group of well nourished children.

The results cannot be explained fully on the basis of present knowledge of dental caries.

Hillman Hospital.

30. Kniesner, A. H.; Mann, A. W., and Spies, T. D.: Relationship of Dental Caries to Deficiencies of the Vitamin B Group, J. Dent. Research **21**:259 (June) 1942.

31. Dreizen, S.; Mann, A. W.; Cline, J. K., and Spies, T. D.: The Buffer Capacity of Saliva as a Measure of Dental Caries Activity, J. Dent. Research **25**: 213 (Aug.) 1946.

DETERMINATION OF ANTI-RH ANTIBODY IN INFANTS WITH ERYTHROBLASTOSIS FETALIS

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THE RELATION of Rh incompatibility to erythroblastosis fetalis [1] has been generally accepted. The disease is caused by the combination of the maternal anti-Rh antibody with the Rh antigen contained in the fetal tissue. The immunologic diagnosis of erythroblastosis fetalis, therefore, should rest on the demonstration of such an antigen-antibody combination in the fetus. Haberman and Hill [2] and Carter and Loughrey [3] utilized the reversible nature of the antigen-antibody reaction to liberate the agglutinin, or "complete" antibody,[4] from the baby's washed red blood cells in some, but not all cases. It must be noted, however, that there are two types of maternal antibody, the complete

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This work was aided by a grant from the Ohio State Department of Public Welfare, Division of Mental Hygiene, Bureau of Prevention and Education.

1. The term "erythroblastosis fetalis," while admittedly not ideal, has been used in this paper because of its priority. The newer terms, "acute hemolytic anemia of the newborn" and "hemolytic disease of the newborn," have been purposely avoided because they imply that the disease state is the direct result of hemolysis, a point which may be disputed.

2. Haberman, S., and Hill, J. M.: The Clinical Significance of the Rh Factor: II. Its Importance in Erythroblastosis Fetalis, Texas State J. Med. **40**:182 (July) 1944.

3. Carter, B. B., and Loughrey, J.: A Method of Demonstrating Anti-Rh Agglutinins in Cases of Erythroblastosis Fetalis, Am. J. Clin. Path. **15**:575 (Dec.) 1945.

4. Without any implication as to the structure of the antibody-globulin molecule, the term "complete" antibody is used here to indicate one which gives a visible agglutination in the usual system, using isotonic solution of sodium chloride as a diluent, as well as in albumin or serum. The term "incomplete" antibody is used to indicate one which gives a visible agglutination only when the water content of the system has been kept low by the use of serum or albumin as a diluent (Diamond and Denton).[5] This phenomenon has been associated with antibodies described under a variety of names, such as "conglutinating," "univalent," "blocking" and "mature." These two types of antibodies may or may not eventually prove to be separate and distinct.

and the incomplete. The sensitized mother may transfer to her fetus the type or types of antibody which her serum contains. With the use of a similar technic, our results have agreed with those of the aforementioned workers, and we have extended our observations to take into account both types of antibody. Refinements in technic now make it possible to establish a positive diagnosis of erythroblastosis fetalis by the liberation of anti-Rh antibody from the baby's red cells.

PRESENT INVESTIGATION

Methods.—The complete antibody was detected by the agglutination method of Levine and Stetson.[5]

The incomplete antibody was detected by the conglutination test of Wiener.[6] This was supplemented in many instances by the slide test of Diamond and Abelson.[7] Determination of titers of the incomplete antibody was made by the albumin dilution technic of Diamond and Denton.[8]

A precise and delicate method of proving the presence of the weak and incomplete anti-Rh antibody has been brought forth by Coombs, Mourant and Race.[9] Their method involves reaction of weak anti-Rh serum with Rh-positive cells. These red cells adsorb the antibody globulin but do not agglutinate. They can then be made to coalesce on the addition of rabbit anti-human-globulin. By the selection of appropriate test cells and control cells, extremely small amounts of the antibody may be demonstrated, either free or adsorbed onto cells. Hill and Haberman[10] applied the term "developing test" to this procedure.

Experimental Procedures.—The optimum conditions for release of antibody were studied on cells exposed to anti-Rh antibody in vitro. The following experiments were carried out in parallel, using Rh-negative and Rh-positive red cells.

Packed, washed red cells were added to from 4 to 8 volumes of anti-Rh serum (complete) of the same OAB group. These were incubated at 37 C. for thirty minutes and then refrigerated at 5 C. for an additional thirty minutes. The cells were packed by centrifuging; the serum was removed, and the cells were washed

5. Levine, P., and Stetson, R. E.: An Unusual Case of Intragroup Agglutination, J. A. M. A. **113**:126 (July 8) 1939.

6. Wiener, A. S.: Conglutination Test for Rh Sensitization, J. Lab. & Clin. Med. **30**:662 (Aug.) 1945.

7. Diamond, L. K., and Abelson, N. M.: The Demonstration of Anti-Rh Agglutinins: An Accurate and Rapid Slide Test, J. Lab. & Clin. Med. **30**:204 (March) 1945.

8. Diamond, L. K., and Denton, R. L.: Rh Agglutination in Various Media with Particular Reference to the Value of Albumin, J. Lab. & Clin. Med. **30**:821 (Oct.) 1945.

9. Coombs, R. R. A.; Mourant, A. E., and Race, R. R.: A New Test for the Detection of Weak and "Incomplete" Rh Agglutinins, Brit. J. Exper. Path. **26**:255 (Aug.) 1945.

10. Hill, J. M., and Haberman, S.: Demonstration of Rh Antibodies in the Newborn and Further Evidence of the Pathogenesis of Erythroblastosis, J. Lab. & Clin. Med. **31**:1053 (Oct.) 1946.

four times with ice cold 0.85 per cent solution of sodium chloride. The packed sensitized cells were resuspended in 3 volumes of the saline solution and placed in the water bath with intermittent agitation. The various periods of time the samples were kept in the bath and the temperatures to which they were subjected will be discussed later. After this treatment with heat, the cells were centrifuged rapidly at the same temperature and the supernatant was removed while the contents were still warm. The supernatant was tested for its agglutinin content against Rh_1Rh_2 cells and against Rh-negative cells of the same OAB group. One drop of a 2 per cent suspension of red cells in saline solution was added to 2 drops of supernatant. The amount of agglutination was read in the usual manner after incubation for one-half hour at 37 C. and another centrifugation.

The saline washings obtained before treatment with heat were tested for agglutinin content; in each case the last two of the four washings showed no visible reaction. Agglutinin was liberated only from Rh-positive cells.

The duration of the heat treatment was found to be important in relation to the amount of antibody released. An increasing amount of agglutinin was released with from ten up to forty minutes of the heat treatment, accompanied with an increase in the amount of hemolysis. The actual temperature of the water bath, in the range of from 45 to 55 C. during the heat treatment, was found to have little influence on the amount of the antibody released, but the amount of hemolysis was much less pronounced at 50 C. or below. The p_H of the saline solution used during the heat treatment was varied from 6.3 to 7.8.

It was concluded that release of antibody was best accomplished when the cells were suspended in a saline solution of p_H 7.0 and incubated at 45 to 50 C. for a period of from thirty to forty minutes.

When anti-Rh serum containing only incomplete antibodies was permitted to react with Rh-positive cells, no agglutinin could be demonstrated in the final saline supernatant. However, when a 20 per cent solution of bovine albumin was used in place of the saline solution during the period of heat treatment, clumping of Rh-positive cells could be demonstrated with the final (albumin) supernatant. By this means, conditions comparable to those pointed out by Diamond and Denton [8] as necessary for demonstration of the incomplete anti-Rh antibody were met.

Clinical Application.—In applying this test to the detection of anti-Rh antibody in babies with erythroblastosis, 2 cc. of the patient's citrated blood was used. The red cells were separated from the serum and washed four times with ice cold isotonic solution of sodium chloride. These packed cells were then divided into two equal portions, one of which was resuspended in 3 volumes of saline solution, the other in a similar amount of a 20 per cent solution of bovine albumin. Both portions were subjected to the heat treatment outlined in the previous section.

To date, this procedure has been successful in liberating the antibody from the blood in 10 of 11 cases of erythroblastosis fetalis. In 1 case the baby was not observed until the age of 16 days, at a time when the baby's hemoglobin was no longer diminishing. The mother's serum contained both complete and incomplete antibodies in titers of 1:512 and 1:16,384, respectively. No antibody was liberated from the baby's cells in either the saline or the albumin solution. Of the mothers in the 10 remaining cases, the serums of 3 contained both the complete and the incomplete antibodies, and in the serums of 7 only incomplete antibodies could be detected. With the exception of the first case cited, the antibody was liberated from the cells of all the babies. The albumin supernatant in each case gave a positive reaction to the conglutination test with Rh-positive cells but not with Rh-negative cells. In no case did the saline supernatant give any observable agglutination; however, in 6 cases when Rh-positive cells were allowed to incubate in these saline supernatants the cells became sensitized with anti-Rh antibody, as could be demonstrated on the addition of anti-human-serum. The pertinent details are shown in the table.

Wiener and Sonn [11] first mentioned the use of anti-human-serum to demonstrate the presence of sensitized cells in a baby with erythroblastosis. Coombs, Mourant and Race [9] and Hill and Haberman [10] have confirmed their observation in several instances. As can be seen in the table, we were able to demonstrate sensitized cells in all but 1 case in which the test was used. It might be mentioned that none of the other tests we have used gave the distinctly positive reactions as the one here outlined when potent anti-human-serum was used. However, our experience indicated that even when the serum is kept frozen its potency is apt to decrease.

In applying this method to the detection of the anti-Rh antibody in infants with erythroblastosis, the red cells from a few drops of the patient's blood were washed four times with ice cold isotonic solution of sodium chloride. Serum from a rabbit immunized against human serum was diluted 1:20 and absorbed several times with Rh_1 Rh_2 red cells of the same OAB blood group as the baby's until the serum would no longer agglutinate the absorbing cells. The highest dilution of the serum after absorption which would precipitate human serum was 1:90. One drop of a 2 per cent suspension of the baby's washed cells in 0.85 per cent solution of sodium chloride was added to 2 drops of the absorbed rabbit anti-human-serum. The mixture was allowed to stand at room temperature for twenty minutes, then centrifuged, and the sediment examined for agglutination. Controls of Rh-positive cells from the blood of babies without erythroblastosis and of Rh-negative cells were included, all uniformly showing no agglutination.

Antibodies can also be demonstrated convincingly in the serum of a baby with erythroblastosis by adding 1 drop of a 2 per cent suspension

11. Wiener, A. S., and Sonn, E. B.: Pathogenesis of Congenital Hemolytic Disease (Erythroblastosis Fetalis): II. Illustrative Case Histories of Rh Sensitization, Am. J. Dis. Child. **71**:25 (Jan.) 1946.

of Rh_1 Rh_2 cells to 2 drops of the baby's serum. Rh-negative cells were similarly treated as a control. After one-half hour under refrigeration, the cells were washed three times in ice cold saline solution and resuspended in 2 drops of absorbed rabbit anti-human-serum. * After standing twenty minutes the results were read, as mentioned previously.

Details of Tests in Eleven Cases of Erythroblastosis Fetalis

Cases		Age of Baby	Anti-Rh Antibody in Serum: Titer in Saline Solution	Anti-Rh Antibody in Serum: Titer in Albumin	Anti-Rh Antibody in Serum: CMR	Release of Antibody from Cells: Saline Solution	Release of Antibody from Cells: Albumin	Sensitized Cells (CMR)	Severity of Disease	Treatment	Outcome
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	Baby	6 days	—	—	*						
Ba.....	Mother	.....	1:512	1:16,384	*	—(agg)/*(CMR)	—	*	Mild	Repeated transfusions of Rh-negative blood	Recovery
	Baby	16 days	—	—	*						
Fa.....	Mother	.....	1:1	1:512	*	—(agg)/*(CMR)	+	+	Mild	Repeated transfusions of Rh-negative blood	Recovery
	Baby	3 wk.	—	>1:1†	+						
Tib.....	Mother	.....	—	1:256	*	—(agg)/+(CMR)	+	+	Severe	Repeated transfusions of Rh-negative blood	Death from kernicterus
	Baby	1 hr.	—	—	+						
Kim.....	Mother	.....	—	1:64	+	—(agg)/+(CMR)	+	+	Hydrops	.....	Stillbirth
	Baby	Stillbirth	—	—	+						
Mein.....	Mother	.....	—	1:128	+	—(agg)/+(CMR)	+	+	Moderate	Repeated transfusions of Rh-negative blood	Recovery
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Rich.....	Mother	.....	—	1:640	+	—(agg)/+(CMR)	+	+	Hydrops	.....	Death in 1½ hr.
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In 7 specimens tested in this manner, all gave 4 plus reactions, indicating the presence of anti-Rh antibody in the baby's serum.

These procedures may be used to refute, as well as to establish, a diagnosis of erythroblastosis. The following case illustrates the value of being able to make a positive diagnosis of erythroblastosis.

REPORT OF A CASE

A specimen of cord blood, which had been refrigerated two days, was sent to us from another hospital for antibody studies, together with the following data:

Mrs. F. had had four previous pregnancies. The first pregnancy (1938) resulted in the birth of a normal boy. The second pregnancy terminated in a stillbirth. The third pregnancy resulted in the birth of a boy, who died at the age of 5 days. The fourth pregnancy (1944) resulted in the birth of a normal girl.

During her fifth pregnancy, blood studies revealed Mrs. F. to be Rh negative (her husband was Rh positive). The "anti-Rh antibody titer" in her serum was reported to be 1:1,550 at the end of seven and one-half months' gestation. At this time a decrease in fetal movements was noted and it seemed advisable to deliver the baby. A classic cesarean section was performed four weeks before term. A jaundiced female infant, weighing 2,695 Gm., was delivered, and the mother was sterilized. The child had episodes of cyanosis shortly after birth and was given oxygen continuously. Laboratory tests showed the baby to be Rh positive. The hemoglobin was 15.36 Gm. per hundred cubic centimeters forty-eight hours after delivery. There was 1 nucleated red cell per hundred white blood cells. A diagnosis of erythroblastosis was made.

In our laboratory, the two procedures previously described were performed immediately on arrival of the specimen of cord blood in order to carry out the tests in parallel with those on the blood of another baby suspected of having erythroblastosis. No anti-Rh antibody could be released from baby F's cells, and the Coombs, Mourant and Race test did not show the baby's cells to be sensitized. Both tests gave strongly positive reactions with the cells of the other baby. This provided a control experiment showing that the technic was dependable. We therefore concluded that Baby F. did not have erythroblastosis fetalis. At this point it was discovered that Baby F. was Rh negative to a number of different anti-Rh typing serums. We advised against transfusion in the case of this infant, and the subsequent clinical course did not exhibit the usual features of erythroblastosis.

It is understandable that the physician made a diagnosis of erythroblastosis in this case. The mother's history of previous obstetric difficulties due to Rh incompatibility was confirmed by the laboratory data. The early appearance of jaundice and cyanosis in the baby, together with the erroneous Rh typing of the cells, made the diagnosis of erythroblastosis seem certain.

It is quite apparent that in cases of this sort the clinician needs an accurate laboratory method to tell him whether the baby's tissues have been acted on by the maternal anti-Rh antibody. It should be pointed out that the demonstration of antibody in the serum of Baby F. would not have indicated fetal Rh incompatibility, but would have pointed only to the passive transfer of a maternal antibody against which the baby had no antigen. Conclusions should be drawn only from the data derived with the baby's cells.

COMMENT

Heretofore, immunologic data could merely imply the diagnosis of erythroblastosis from the demonstration of anti-Rh antibody in an Rh-negative mother delivered of an Rh-positive child. Several case reports have indicated that there may be exceptions. Weiner and Sonn [11] and Hill and Haberman [10] and others have demonstrated incomplete

antibody in the baby's serum, it appears likely that the tissue cells themselves are also exposed to damage from antibodies. This concept would supply an explanation for the evidence of damage to the baby as a whole, which cannot be explained on the basis of hemolysis alone.

SUMMARY

1. A method for liberation of anti-Rh antibody by heat from its combination with the red cells of a baby with erythroblastosis is described. The method will demonstrate both the complete and the incomplete type of antibody.

2. Observations with the method for the demonstration of red cells sensitized with anti-Rh antibody in the blood of babies with erythroblastosis by the use of appropriately absorbed anti-human-serum are described in detail.

3. The use of these methods for verifying the diagnosis of erythroblastosis, using the baby's blood alone, is emphasized.

4. The significance of the reversibility of the antigen-antibody reaction, and the possibility that a damaging antigen-antibody reaction might exist in tissues other than blood cells is discussed in relation to the pathogenesis of erythroblastosis.

NOTE.—Since submitting this paper for publication, we have had the opportunity to observe 20 other infants with erythroblastosis. Anti-Rh antibody was liberated according to the method described in this paper in 19 of the 20 cases. In 1 case the baby was not observed until the ninth day, when the hemolytic process had apparently run its course; no antibody could be liberated.

In accordance with a suggestion by Levine, in 5 cases a solution containing 1 part of LePage's "household glue" (no. 10) in 6 parts of isotonic solution of sodium chloride was compared with a 20 per cent solution of bovine albumin as a medium for the release of antibodies. In each case the agglutination of the test cells was more rapid and complete in the glue solution. In our last 5 cases the glue solution was used in preference to the albumin.

Children's Hospital.

CHEMICAL STUDIES IN CHILDREN WITH THE NEPHROTIC SYNDROME

SIDNEY P. GOTTFRIED, Ph.D.

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THE BLOOD chemistry in nephrosis has been extensively studied by many investigators. Recent advances in knowledge of protein and lipid metabolism and parenteral replacement of protein have suggested new approaches to this still refractory disorder. In the light of this newer knowledge, we have attempted to reexamine the chemical data obtained during the course of the disease, to correlate these results with the clinical observations and to evaluate the effect of various therapeutic agents on the clinical and chemical course of the disease.

Ten patients presenting the nephrotic syndrome were studied over a period of two years, and the chemical data observed during the course of the disease are reported here. These patients were children between the ages of 16 months and 5 years, and included 8 boys and 2 girls. The term "nephrosis" is used in this paper to denote a disorder in which albuminuria, hypoproteinemia and edema are the dominant clinical features, but without evidence of progressive renal insufficiency. In the absence of any known unifying etiologic and pathogenetic basis for this disorder, we have been inclined to adopt the broader concepts of Blackman,[1] Peters and Van Slyke[2] and others, who expressed the opinion that transient hematuria, hypertension or azotemia is not inconsistent with the diagnosis of "nephrosis." The salient clinical features in each of the 10 cases are presented in table 1. It will be observed that a large proportion of this group of patients have, at one time or another, exhibited a slight microscopic hematuria, rise in blood pressure, or elevation of urea nitrogen in the blood. However, with 1 exception

From the Pediatric Research Laboratory and the Pediatric Department of the Jewish Hospital of Brooklyn.

1. Blackman, S. S., Jr.: Pneumococcal Lipoid Nephrosis and the Relations Between Nephrosis and Nephritis: I. Clinical and Anatomical Studies, Bull. Johns Hopkins Hosp. **55**:1, 1934.

2. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1931, vol. 1.

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antibodies in the serums of erythroblastotic babies by the conglutination, open slide and developing tests. The observation of this antibody in the baby, however, merely reflects the presence of the maternal antibody and contributes nothing to the diagnosis of the disease in the baby unless serum from the mother is not available. Moreover, extreme care must be taken to establish the anti-Rh specificity of such antibodies, as cold agglutinins and false positive reactions due to rouleaux may cause difficulty.

The two methods which are described in detail here now make it possible for the laboratory to make a positive diagnosis of erythroblastosis by examination of the baby's blood alone. Carter and Loughrey [3] proposed their test for this purpose. However, it is obvious that their procedure, as well as that of Hill and Haberman,[10] fails when the maternal serum contains only incomplete antibodies. This obstacle can be circumvented by the employment of albumin in place of saline solution and by the use of the optimum period of incubation and temperature described previously. Carter and Loughrey recognized that it is occasionally impossible to liberate antibodies by heat from the red cells if the child is over 1 week of age; our experience confirms their statement.

In our hands, the reactions obtained with anti-human-serum appeared to be more sensitive, and if the serum becomes generally available this technic may prove to be more satisfactory for the detection of sensitized cells in the baby. However, the positive reaction with anti-human-serum does not give any indication of the specificity of the antibody adsorbed onto the baby's cells. On the other hand, when antibody has been liberated according to our method, it is then possible by means of suitable controls to demonstrate its exact specificity. In a case of icterus precox in which a baby with type A blood became jaundiced, presumably owing to the action of an excessively high anti-A titer in the maternal serum, the use of anti-human-serum gave no evidnece of sensitized cells. This test was performed on the sixteenth day of life. However, until more evidence is accumulated, it must be assumed that this test is not specific for the Rh antibody. Until such time, the liberation of antibodies by the heat method has the advantage of being both rapid and simple.

It can be inferred from the strength of the reaction with maternal serum that the incomplete antibody has combined with the baby's red cells in vivo. The red cells of a baby with erythroblastosis whose mother has complete antibodies in her serum do not agglutinate in the mother's serum in a titer comparable to that of the cells of a normal baby of the same age and Rh subtype. This phenomenon has been observed on many occasions; in general, there has been seen an eightfold reduction of the agglutinating titer of the cells of the erythroblastotic baby from the titer of the control cells. From this it would appear that there is a cer-

tain amount of the incomplete type of antibody adsorbed onto the red cells of a baby with erythroblastosis, necessitating a stronger concentration of agglutinin to cause a visible reaction in a saline system. The red cells in erythroblastosis are not usually saturated with the incomplete antibody; otherwise, numerous instances would occur in which the agglutination would be "blocked" and the baby would appear to be Rh negative.

Thus, a puzzling situation is presented which appears to be at variance with what is known of other antigen-antibody reactions. There are present at birth free antigen in the agglutinable red cells, free antibody in the baby's serum and antibody combined with antigen in the red cells. The fact that the antigen and the antibody may be easily dissociated from their combination by physical means indicates that the explanation for this unusual situation lies in the low avidity of the antibody for the Rh antigen, rather than in the action of an inhibiting factor, as suggested by Bloxsom.[12]

The amount of anti-Rh antibody in the baby at birth has been shown to be sufficient to accomplish the destruction of his entire supply of (Rh-positive) red cells. There still remains at birth, in certain instances, a demonstrable excess of antibody. We have on several occasions observed that the amount of Rh-positive blood required to maintain a satisfactory hemoglobin concentration in the baby may be several times the calculated blood volume of the infant. In 1 instance, an amount of blood equivalent to five times the original volume was required.

It would appear possible that after an Rh-positive cell is damaged, anti-Rh antibody may be released in vivo to attack fresh Rh-positive red cells introduced into the circulation. If this is true, it may not be possible to bind the antibody to fresh red cells permanently.

This fact assumes importance when considered in the light of the proposal of Danis, Eto and Sennott[13] to transfuse into babies with erythroblastosis preferably Rh-positive blood in order that it may combine with and neutralize the excess anti-Rh antibody so as to protect the infant's own red cells from further damage.

The question is of more than theoretic interest, since, with the evidence presented by Boorman and Dodd[14] that Rh antigen is present in the tissues other than red cells, and with the demonstration of free

12. Bloxsom, A.: Hemolytic Disease of the Newborn (Erythroblastosis Fetalis): Treatment by a Single Massive Transfusion, with Complete Recovery, Am. J. Dis. Child. **72**:320 (Sept.) 1946.

13. Danis, P. G.; Eto, J. K., and Sennott, J. S.: The Use of Rh Positive Blood Cells in the Treatment of Erythroblastosis Fetalis, J. Pediat. **28**:457 (April) 1946.

14. Boorman, K. E., and Dodd, B. E.: Group-Specific Substances A, B, M, N and Rh: Their Occurrence in Tissues and Body Fluids, J. Path. & Bact. **55**:329 (July) 1943.

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Ten patients presenting the nephrotic syndrome were studied over a period of two years, and the chemical data observed during the course of the disease are reported here. These patients were children between the ages of 16 months and 5 years, and included 8 boys and 2 girls. The term "nephrosis" is used in this paper to denote a disorder in which albuminuria, hypoproteinemia and edema are the dominant clinical features, but without evidence of progressive renal insufficiency. In the absence of any known unifying etiologic and pathogenetic basis for this disorder, we have been inclined to adopt the broader concepts of Blackman,[1] Peters and Van Slyke[2] and others, who expressed the opinion that transient hematuria, hypertension or azotemia is not inconsistent with the diagnosis of "nephrosis." The salient clinical features in each of the 10 cases are presented in table 1. It will be observed that a large proportion of this group of patients have, at one time or another, exhibited a slight microscopic hematuria, rise in blood pressure, or elevation of urea nitrogen in the blood. However, with 1 exception

From the Pediatric Research Laboratory and the Pediatric Department of the Jewish Hospital of Brooklyn.

1. Blackman, S. S., Jr.: Pneumococcal Lipoid Nephrosis and the Relations Between Nephrosis and Nephritis: I. Clinical and Anatomical Studies, Bull. Johns Hopkins Hosp. **55**:1, 1934.

2. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1931, vol. 1.

TABLE 1.—*Summary of Clinical Data in Ten Cases of Nephrosis*

Patient	A. C.	M. C.	M. G.	R. K.	W. K.	A. P.	B. P.	J. P.	D. S.	A. Z.
Sex	Male	Male	Male	Male	Male	Female	Female	Male	Male	Male
Race	White	White	White	White	White	White	White	White	White	White
Age at onset	21 mo.	3 yr. 7 mo.	3 yr.	2 yr.	17 mo.	3 yr.	3 yr.	3 yr.	16 mo.	22 mo.
Past history										
Serious illnesses, infectious diseases, allergies, chemotherapy, etc.	None	Frequent mild colds; urticaria (food allergy)	Thrush at birth; rubeola and rubella at 8 mo.; tonsillitis at 2½ yr.	None	Pneumonia at 9 mo.; sulfadiazine	Pyelitis at 4-5 mo.; frequent colds	Group at 6 wk.; severe infantile eczema due to milk allergy; sulfadiazine	Pneumonia at 8 mo.; frequent tonsillitis	None	Recurrent tonsillitis and diarrhea since 2 mo. of age; sulfadiazine
Operations	None	T & A* 1½ yr. prior to onset	None	None	None	T & A* at 1½ yr.	T & A at 2 yr. (2 mo. prior to onset)	T & A* at 3 yr. (3-4 mo. prior to onset)	None	None
Present illness										
Recent infection	None	None	None	Cough and cold 2-3 mo. prior to onset	Sore throat 1 day prior to onset	None	Cold and diarrhea a few days prior to onset	Rhinitis 1 wk. prior to onset	None	Tonsillitis 2 mo. prior to onset
Presenting symptoms	Diarrhea; facial edema	Generalized edema; oliguria	Facial edema	Facial and generalized edema; oliguria	Facial and generalized edema; fever	Facial edema	Facial edema; fever	Edema; fever; diarrhea	Generalized edema; vomiting; diarrhea	Facial edema; vomiting; abdominal pain
Clinical findings										
Edema	4 plus	4 plus	4 plus	4 plus	4 plus	4 plus	4 plus	4 plus	4 plus	4 plus
Albuminuria	3 to 4 plus	3 to 4 plus	3 to 4 plus	2 to 4 plus	3 to 4 plus	2 to 4 plus	2 to 3 plus	3 to 4 plus	3 to 4 plus	3 to 4 plus

Cylindruria	None	Occasional hyaline cast	Moderate hyaline and fine granular casts	Rare to occasional granular casts	Occasional to many hyaline and granular casts	None	Red blood cells, white blood cells and granular casts	Granular and hyaline casts	Occasional to many fine granular and hyaline casts	Occasional to moderate granular and hyaline casts
Hematuria	0 to 100/ high power field	0 to 1/ high power field	Occasional red blood cells	None	Occasional to 10/high power field	None	1-12/high power field consistently	0-2/high power field	0-5/high power field	Occasional to many (transfusion r.)
Blood pressure										
Minimum	106/80	110/70	90/62	110/82	90/70	106/68	104/60	106/76	106/ 50	100/ 60
Maximum	144/96	136/96	130/90	142/80	140/96	132/90	140/90	130/98	170/130	142/120
Mean	124/85	120/75	120/80	120/80	116/83	122/79	120/80	122/85	120/ 80	120/ 90
Blood urea nitrogen, mg./ 100 cc.										
Minimum	12.8	8.0	7.0	6.1	8.0	....	12.0	16.0	7.2	10.2
Maximum	20.3	34.6	39.1	26.0	42.2	....	43.5	44.0	56.4	37.0
Mean	15.7	19.9	13.5	14.2	20.7	14.0	20.5	26.7	32.9	18.6
Hemoglobin, Gm./100 cc.	14.3	12.0	11.7	12.5	11.0	12.0	12.6	10.5	10.0	10.4
Course										
Number of attacks	1	2	1	3	4	2	4	4	5	5
Duration of attacks	5 mo.	4 mo.	10 mo.	3 wk. to 4 mo.	2 wk. to 7 mo.	3 to 4 wk.	2 wk. to 7 mo.	1 wk. to 4 mo.	4-5 mo.	4-7 mo.
Length of remissions	.....	6 mo.	.....	2 wk. to 2 mo.	2-4 wk.	4 wk.	6 wk.	1 mo. to 1 yr.	3-5 mo.	2 wk. to 4 mo.
Total duration	5 mo.	10 mo.	10 mo.	12 mo.	15 mo.	4 mo.	15 mo.	2½ yr.	22 mo.	27 mo.
Result	Unchanged	Unchanged	Unchanged	Improved	Unchanged	Unchanged	Unchanged	Died	Died	Improved

* Tonsillectomy and adenoidectomy.

(D. S.), none has shown any evidence of progressive renal failure. Patient D. S. presented a nephrotic picture at the onset of his illness, but subsequently showed unmistakable symptoms of chronic glomerulonephritis, with marked and persistent hypertension, cardiac enlargement and insufficiency and a terminal uremia.

METHODS

The patients were observed in the hospital over periods of two to seventeen months. Frequent blood chemical determinations were made, in addition to the usual hematologic and urinary examinations. All patients were weighed daily. The blood pressure was recorded on alternate days in most cases.

There follows a résumé of the chemical methods employed in this study: Serum proteins were determined by the micro Kjeldahl method.[3] Serum albumin was determined similarly after precipitating the globulin with 22.2 per cent sodium sulfate.[4] Fibrinogen was determined by forming the fibrin clot and determining its nitrogen content by the micro Kjeldahl method.[4] Amino acids were determined colorimetrically using sodium beta-naphthoquinone-4-sulfonate.[5] Nonprotein nitrogen was determined by the micro Kjeldahl method after the proteins had been precipitated.[6] Urea nitrogen was determined by treating the serum with urease and aerating over the ammonia.[7] Uric acid was determined colorimetrically by means of phosphotungstic acid.[8] Total lipids were determined gravimetrically.[9] Lipid phosphorus was determined by digesting the serum lipids and analyzing colorimetrically for inorganic phosphorus according to the method of Fiske and Subbarow.[10b] Total cholesterol was determined colorimetrically by the Liebermann-Burchard reaction.[11] Free cholesterol was precipitated with digitonin and deter-

3. (*a*) Lauro, M. F.: Use of Selenium as a Catalyst in the Determination of Nitrogen by the Kjeldahl Method, Indust. & Engin. Chem. (Anal. Ed.) **3**:401, 1931. (*b*) Sobel, A. E.; Yuska, H., and Cohen, J.: A Convenient Method of Determining Small Amounts of Ammonia and Other Bases by the Use of Boric Acid, J. Biol. Chem. **118**:443, 1937.

4. Footnote 3. Howe, P. E.: The Determination of Proteins in Blood: A Micro Method, J. Biol. Chem. **49**:109, 1921.

5. Frame, E. G.; Russell, J. A., and Wilhelmi, A. E.: The Colorimetric Estimation of Amino Nitrogen in Blood, J. Biol. Chem. **149**:255, 1943.

6. Lau.o.[3a] Reis, F., and Powers, H. H.: Selenium as a Catalyst in the Determination of Nonprotein Nitrogen in Blood, J. Lab. & Clin. Med. **20**:1204, 1935.

7. Sobel, A. E.; Mayer, A. M., and Gottfried, S. P.: A Convenient Titrimetric Ultramicromethod for the Estimation of Urea and Kjeldahl Nitrogen, J. Biol. Chem. **156**:355, 1944.

8. Brown, H.: The Determination of Uric Acid in Blood, J. Biol. Chem. **68**:123, 1926.

9. Bloor, W. R.: The Determination of Small Amounts of Lipids in Blood Plasma, J. Biol. Chem. **77**:53, 1928.

10. (*a*) Gottfried, S. P.: Unpublished method. (*b*) Fiske, C. H., and Subbarow, Y.: The Colorimetric Determination of Phosphorous, J. Biol. Chem. **66**:375, 1925.

11. Kaye, I. A.: Determination of Total and Free Cholesterol in Blood Serum, J. Lab. & Clin. Med. **25**:9, 1940.

mined by the Lieberman-Burchard reaction.[12] Calcium was precipitated as the oxalate, converted to the carbonate by heat, and determined by titration.[13] Phosphorus was determined colorimetrically.[10b] Alkaline phosphatase was determined by the procedure of Bodansky.[14] Vitamin A was determined by the Carr-Price reaction, as modified by May and his co-workers.[15] Carotene was determined by extracting with petroleum ether and measuring the intensity of the yellow pigment.[16] Glucose was determined colorimetrically by the Folin-Wu method.[17] Amylase was determined by the method of Somogyi.[18] Prothrombin time was determined according to the method of Quick.[19] The cephalin flocculation test was performed according to the method of Hanger.[20] The thymol turbidity test was performed according to the method of Shank and Hoagland.[21] Since the serums examined were cloudy due to lipemia, the cloudiness was corrected for by means of a blank consisting of serum and distilled water in the same proportions employed in the actual determination. The sulfobromophthalein test was performed by injecting 2 mg. of the dye per kilogram of body weight, and measuring the retention at the end of eighteen minutes.[22] Bilirubin was determined colorimetrically by diazotization.[23] Carbon dioxide values were determined by the method of Van Slyke.[24] Chlorides

12. Sobel, A. E., and Mayer, A. M.: Improvements in the Schoenheimer-Sperry Method for the Determination of Free Cholesterol, J. Biol. Chem. **157**:255, 1945.

13. Sobel, A. E., and Sobel, B. A.: Microestimation of Calcium in Serum, J. Biol. Chem. **129**:721, 1939.

14. Bodansky, A.: Phosphatase Studies: II. Determination of Serum Phosphatase; Factors Influencing the Accuracy of the Determination, J. Biol. Chem. **101**:93, 1933.

15. May, C. D.; Blackfan, K. D.; McCreary, J. F., and Allen, F. H., Jr.: Clinical Studies of Vitamin A in Infants and Children, Am. J. Dis. Child. **59**:1167 (June) 1940.

16. Clausen, S. W., and McCoord, A. B.: The Determination of Carotene and Xanthophyll by a Single Distribution Between Liquid Phases, J. Biol. Chem. **113**:89, 1936.

17. Folin, O., and Wu, H.: A Simplified and Improved Method for the Determination of Sugar, J. Biol. Chem. **41**:367, 1920.

18. Somogyi, M.: Micromethods for the Estimation of Diastase, J. Biol. Chem. **125**:399, 1938.

19. Quick, A. J.: The Nature of the Bleeding in Jaundice, J. A. M. A. **110**:1658 (May 14) 1938.

20. Hanger, F. M.: Serological Differentiation of Obstructive from Hepatogenous Jaundice by Flocculation of Cephalin-Cholesterol Emulsions, J. Clin. Investigation **18**:261, 1939.

21. Shank, R. E., and Hoagland, C. L.: A Modified Method for the Quantitative Determination of the Thymol Turbidity Reaction of Serum, J. Biol. Chem. **162**:133, 1946.

22. MacDonald, D.: Practical and Clinical Test for Liver Reserve, Surg., Gynec. & Obst. **69**:70, 1939.

23. Hoffman, W. S.: Photelometric Clinical Chemistry, New York, William Morrow & Company, 1941, chap. 22.

24. Van Slyke, D. D., and Cullen, G. E.: Studies of Acidosis: II. A Method for the Determination of Carbon Dioxide and Carbonates in Solution, J. Biol. Chem. **19**:211, 1914.

were determined by titrating the protein-free filtrate with mercuric nitrate, diphenylcarbazone being used as the indicator.[25]

OBSERVATIONS

A. Studies of Blood Chemistry.—The chemical data concerning the blood observed during the course of the disease are listed in table 2.

TABLE 2.—*Data on the Chemical Composition*

Patient	Values	Serum Proteins, Gm./100 Cc.	Serum Albumin, Gm./100 Cc.	Serum Globulin, Gm./100 Cc.	Albumin-Globulin Ratio	Plasma Fibrinogen, Gm./100 Cc.	Nonprotein Nitrogen (Serum), Mg./100 Cc.	Urea Nitrogen (Serum), Mg./100 Cc.
A. C.	Minimum	3.09	0.82	2.05	0.31	....	....	12.8
	Maximum	4.87	1.48	3.41	0.60	....	....	20.3
	Mean	(6)* 3.73	(6) 1.12	(6) 2.61	(6) 0.42	(1) 0.37	(1) 32.4	(3) 15.7
M. C.	Minimum	3.70	0.63	1.94	0.22	....	....	8.0
	Maximum	4.44	1.86	3.55	1.00	....	....	34.6
	Mean	(9) 4.10	(8) 1.25	(8) 2.84	(8) 0.50	(1) 0.83	(0)	(11) 19.9
M. G.	Minimum	3.36	0.50	2.09	0.15	....	32.0	7.0
	Maximum	3.80	2.16	4.04	1.03	....	63.0	39.1
	Mean	(20) 4.08	(19) 1.21	(19) 2.86	(19) 0.44	(1) 0.76	(4) 44.2	(12) 13.5
R. K.	Minimum	3.17	0.60	2.02	0.23	....	31.2	6.1
	Maximum	4.69	1.88	3.25	0.81	....	46.1	26.0
	Mean	(12) 3.78	(11) 1.19	(11) 2.59	(11) 0.40	(1) 0.95	(4) 36.2	(11) 14.2
W. K.	Minimum	3.03	0.58	1.72	0.19	....	31.0	8.0
	Maximum	4.41	2.28	2.98	1.10	....	120.0	42.2
	Mean	(18) 3.47	(18) 0.94	(18) 2.55	(18) 0.41	(0)	(4) 60.1	(12) 20.7
A. P.	Minimum	3.88	1.75	2.15	0.62	....	20.0	....
	Maximum	4.14	1.61	2.51	0.87	....	21.0	....
	Mean	(2) 4.01	(2) 1.68	(2) 2.33	(2) 0.70	(1) 0.86	(2) 20.5	(1) 14.0
B. P.	Minimum	2.96	0.35	1.82	0.12	....	32.1	12.0
	Maximum	4.23	1.99	3.01	0.90	....	80.7	43.5
	Mean	(20) 3.46	(20) 1.16	(20) 2.30	(20) 0.53	(20) 0.86	(5) 48.4	(12) 20.5
J. P.	Minimum	3.26	0.57	2.18	0.22	....	37.1	16.0
	Maximum	3.96	1.31	2.92	0.51	....	68.3	44.0
	Mean	(9) 3.09	(8) 1.04	(8) 2.43	(8) 0.43	(1) 0.68	(2) 53.2	(3) 26.7
D. S.	Minimum	2.90	0.46	1.53	0.20	....	39.6	7.2
	Maximum	5.44	2.64	3.17	1.60	....	79.0	56.4
	Mean	(21) 3.72	(18) 1.80	(18) 2.22	(18) 0.71	(0)	(7) 65.2	(21) 32.9
A. Z.	Minimum	3.17	0.37	1.39	0.12	....	28.0	10.2
	Maximum	6.33	3.14	3.19	2.10	....	36.4	37.0
	Mean	(36) 3.79	(35) 1.34	(35) 2.44	(35) 0.60	(0)	(6) 31.9	(26) 18.6

* Numbers in parentheses represent the number of determinations performed. † Fasting.

If several determinations were made, minimum, maximum and mean values for each patient are presented, together with the number of determinations done.

The values obtained for total serum protein, serum albumin and the albumin-globulin ratio were consistently low, as is characteristic of this disease. The serum globulin values were normal or but slightly

25. Schales, O., and Schales, S. S.: A Simple and Accurate Method for the Determination of Chloride in Biological Fluids, J. Biol. Chem. **140**:879, 1941.

decreased. Fibrinogen values were all elevated, and a correlation was noted between the high fibrinogen values and the increased erythrocyte sedimentation rates in these patients, as previously pointed out by Luetscher.[26]

Although these patients had at times an increase in the nonprotein nitrogen and urea nitrogen of the blood, the transient nature of this

Ten Children with the Nephrotic Syndrome

Total Lipids (Serum), Mg./100 Cc.	Total Cholesterol (Serum), Mg./100 Cc.	Free Cholesterol (Serum), Mg./100 Cc.	Lipid Phosphorus (Serum), Mg./100 Cc.	Calcium (Serum), Mg./100 Cc.	Inorganic Phosphorus (Serum), Mg./100 Cc.	Chlorides (Serum), Mg./100 Cc.	CO_2 Content (Serum), Volume per Cent	Glucose (Serum), Mg./100 Cc.	Glucose Tolerance (Capillary Blood), Mg./100 Cc.
									F.† 128
.....	544	130	....	3.6	4.4	...	....	115	1 hr. 132
.....	800	186	....	7.3	5.6	...	....	128	2 hr. 142
(1) 1,520	(4) 649	(4) 158	(1) 9.0	(5) 5.5	(3) 4.9	(1) 355	(1) 41.8	(2) 122	3 hr. 118
									F. 140
.....	555	157	....	7.6	4.4	...	....	109	1 hr. 160
.....	975	226	....	8.8	4.6	...	....	140	2 hr. 180
(1) 1,191	(7) 748	(4) 158	(0)	(2) 8.2	(2) 4.5	(1) 335	(1) 53.1	(2) 125	3 hr. 154
									F. 137
.....	646	149	....	6.6	4.9	...	47.0	...	½ hr. 174
.....	1,140	259	....	9.0	5.6	...	62.0	...	1 hr. 184
(1) 1,932	(9) 860	(8) 219	(1) 12.7	(5) 8.1	(5) 5.3	(1) 349	(2) 55.0	(1) 137	2 hr. 140
									F. 116
1,520	347	105	....	7.7	4.2	366	49.0	...	½ hr. 120
2,990	1,025	262	....	10.0	5.9	372	55.6	...	1 hr. 128
(5) 2,064	(11) 637	(10) 180	(0)	(7) 8.9	(8) 5.0	(2) 369	(3) 53.1	(1) 116	2 hr. 104
									F. 120
1,930	300	107	....	7.9	4.6	...	....	...	½ hr. 114
2,975	800	236	....	9.2	7.1	...	....	...	1 hr. 141
(2) 2,453	(9) 578	(7) 175	(1) 16.0	(3) 8.3	(4) 5.6	(1) 355	(1) 55.4	(1) 120	2 hr. 100
									F. 116
.....	645	...	....	7.5	4.1	...	....	116	½ hr. 176
.....	890	...	....	8.7	5.2	...	....	119	1 hr. 145
(1) 1,775	(2) 767	(1) 194	(1) 12.3	(2) 8.1	(2) 4.7	(1) 384	(0)	(2) 118	2 hr. 132
									F. 118
1,637	455	116	....	5.9	4.9	304	46.4	...	½ hr. 132
3,613	842	348	....	10.7	6.8	336	75.2	...	1 hr. 188
(3) 2,317	(12) 574	(9) 185	(1) 22.4	(11) 7.7	(12) 6.2	(2) 345	(4) 57.0	(1) 120	2 hr. 123
									F. 120
.....	661	133	....	6.0	5.3	...	....	...	½ hr. 148
.....	673	167	....	7.3	6.1	...	....	...	1 hr. 144
(1) 2,750	(2) 667	(2) 150	(1) 14.6	(2) 6.7	(2) 5.7	(0) ...	(0)	(1) 118	2 hr. 128
									F. 136
1,550	326	169	....	3.9	4.4	...	32.3	72	½ hr. 142
2,220	1,080	281	....	10.3	7.6	...	42.2	136	1 hr. 188
(3) 1,829	(8) 714	(6) 234	(1) 24.5	(10) 7.9	(10) 5.9	(1) 361	(4) 36.7	(7) 102	2 hr. 190
									F. 96
1,390	348	113	18.6	6.6	3.6	338	....	91	½ hr. 139
3,480	950	305	20.6	9.4	5.3	396	....	96	1 hr. 144
(7) 2,959	(17) 648	(15) 207	(2) 19.6	(5) 8.4	(6) 4.7	(3) 376	(1) 45.6	(3) 92	2 hr. 117

increase and the subsequent return to normal values in all cases but 1 would seem to indicate a relative rather than an absolute renal insufficiency. This transient azotemia may be related to periods of oliguria or considerably increased protein catabolism, as suggested by Peters and Van Slyke.[2] Values for uric acid were essentially normal. Values

26. Luetscher, J. A., Jr.: Electrophoretic Analysis of Plasma and Urinary Proteins, J. Clin. Investigation **19**:313, 1940.

obtained for plasma amino acid nitrogen were either normal or slightly elevated, even during periods of so-called nephrotic crises. This is in disagreement with the observations of Farr and MacFadyen,[27] who reported chronic hypoaminoacidemia, or a sharp drop in plasma amino acids associated with nephrotic crises. We consider a value of 3 to 5 mg. per hundred cubic centimeters for plasma amino acid nitrogen to be normal by the method employed here.

Total lipids and total and free cholesterol were all considerably elevated, in conformity with the usual findings in this disorder. The lipid phosphorus values, on the other hand, were usually normal, or only moderately elevated.

The serum calcium values were consistently low, as has been frequently noted in this disease. No clinical evidence of tetany has been noted in any of these patients. The low calcium values are related to the hypoproteinemia, as indicated by a comparison of the observed values with those calculated from the equation of Peters and Eiserson[28]:

$$\text{Total Ca} = 7 - 0.255\,\text{P} + 0.556\ \text{protein}$$

where calcium and phosphorus are expressed in milligrams per hundred cubic centimeters and protein in grams per hundred cubic centimeters. Although this equation was empirically and statistically derived from observations on adults, and may not apply to children, nevertheless the mean difference between our observed and calculated serum calcium values in forty-eight determinations was only 0.1 mg. per hundred cubic centimeters, with a standard deviation of plus or minus 1.6 mg. per hundred cubic centimeters. In 1 of our patients (A. C.), extremely low calcium values were found, lower, indeed, than might be expected on the basis of his inorganic phosphorus and protein levels. Roentgenographic studies of the long bones made in his case showed a slight degree of generalized osteoporosis, similar to that recently reported by Emerson and Beckman[29] in nephrotic children.

The values obtained for inorganic phosphorus in the serum were essentially normal for this age group. Plasma chlorides and carbon dioxide content were likewise normal for all patients but 1 (D. S.), in whom, as was previously noted, progressive uremia with acidosis developed.

Fasting glucose levels in these nephrotic children were normal or slightly elevated. In 5 of the 10 cases somewhat flattened glucose

27. Farr, L. E., and MacFadyen, D. A.: Hypoaminoacidemia in Children with Nephrotic Crises, Am. J. Dis. Child. **59**:782 (April) 1940.

28. Peters, J. P., and Eiserson, L.: The Influence of Protein and Inorganic Phosphorous on Serum Calcium, J. Biol. Chem. **84**:155, 1929.

29. Emerson, K., Jr., and Beckman, W. W.: Calcium Metabolism in Nephrosis: I. A Description of an Abnormality in Calcium Metabolism in Children with Nephrosis, J. Clin. Investigation **24**:564, 1945.

tolerance curves were obtained, showing a delayed rise, with the peak reaching a value of 150 mg. per hundred cubic centimeters or less. In 4 cases an elevated type of curve, slightly diabetic in form, was obtained. The hyperglycemia occasionally encountered in these children is mild, and the blood sugar levels have not been observed to exceed the renal threshold. Glycosuria is not observed. The elevated glucose tolerance curves do not appear to be related to thyroid medication, as the children showing the tendency toward hyperglycemia had not received thyroid for at least eight weeks prior to the test. Although no explanation can be offered at present for the abnormal glucose tolerance curves observed, the findings suggest some disturbance in the absorption and utilization of glucose in nephrotic children.

In most cases, carotene values were considerably above the normal range of 100 to 200 micrograms per hundred cubic centimeters. This elevation in carotene levels paralleled the degree of lipemia. Josephs [30] has reported similar observations in a variety of conditions associated with lipemia, and has suggested that this correlation may be a simple reflection of the increased capacity of lipemic blood for fat-soluble carotene. On the other hand, vitamin A levels, which were also found to parallel the degree of lipemia in Josephs' study, were elevated only moderately in this group of children, and in about half the cases fell within the normal range of 25 to 60 micrograms per hundred cubic centimeters.

The possible relevance of studies of hepatic function in nephrosis is suggested by recent investigations based on immunologic and electrophoretic methods, which tend to show that the hypoproteinemia of nephrosis may be due to a disturbance in formation of plasma protein, as well as to loss of proteins in the urine. Clinically, 8 of the 10 patients exhibited some degree of hepatomegaly, the edge of the liver being palpable 1.5 to 4.0 cm. below the costal margin. The result of studies of hepatic function are listed in table 3. Neither clinically nor chemically did any of these patients exhibit frank jaundice, although minimal elevations of serum bilirubin were observed in 2 cases. The ratio of free to total cholesterol exceeded the normal range of 20 to 30 per cent at some time in 7 of the patients. The cephalin flocculation test was significantly positive in result (2 plus or more) in 6 cases, and the thymol turbidity values exceeded the normal of 5.0 units in all cases. Serum amylase values were below the normal range of 70 to 140 Somogyi units in 7 cases. Alkaline phosphatase values were below the normal range for this age group in some cases. This observation is not consistent with the other indexes of impaired hepatic function, and no explanation can be offered for it at present. The higher

30. Josephs, H. W.: Studies in Vitamin A: Relation of Vitamin A and Carotene to Serum Lipids, Bull. Johns Hopkins Hosp. **65**:112, 1939.

TABLE 3.—*Studies of Hepatic Function in Ten Children with the Nephrotic Syndrome*

Patient	Values	Free/ Total Cholesterol, Percentage	Cephalin Flocculation	Thymol Turbidity, Units	Sulfobromophthalein Retention, Percentage	Total Serum Bilirubin Mg./ 100 Cc.	Serum Amylase (Somogyi Units)	Alkaline Phosphatase (Bodansky Units)	Prothrombin Time, Seconds	Carotene, Micrograms/ 100 Cc.	Vitamin A, Micrograms/ 100 Cc.
A. C.	Minimum	21.8	...	....	...	....	..	3.3	...	...	....
	Maximum	33.3	...	....	...	....	..	17.3	...	...	....
	Mean (4)*	25.7	(1) 2+	(1) 5.3	(0) ...	(1) 0.16	(1) 84	(3) 8.8	8.8/10.5†	(1) 528	(1) 83.0
M. C.	Minimum	20.3	...	....	...	....	..	3.4	...	...	....
	Maximum	28.3	...	....	...	....	..	5.3	...	...	....
	Mean (7)	25.9	(1) Neg.	(1) 6.3	(1) 0	(1) 0.16	(1) 47	(2) 4.4	7.2/ 6.9†	(1) 1,350	(1) 36.4
M. G.	Minimum	20.1	...	....	...	....	..	3.2	...	...	....
	Maximum	36.3	...	....	...	....	..	3.3	...	...	....
	Mean (8)	26.2	(1) 2+	(1) 24.2	(1) 0	(1) 0.20	(1) 78	(2) 3.3	...	(0) ...	(0) ....
R. K.	Minimum	25.6	...	....	...	....	..	5.2	...	230	26.9
	Maximum	31.9	...	....	...	....	..	7.5	...	913	71.4
	Mean (10)	28.4	(1) 1+	(1) 26.6	(1) Trace	(1) 0.10	(1) 41	(4) 6.3	6.7/ 8.7†	(2) 572	(2) 49.1
W. K.	Minimum	26.2	...	....	...	....	..	3.3	...	...	....
	Maximum	42.7	...	....	...	....	..	5.6	...	...	....
	Mean (7)	34.0	(1) 3+	(1) 14.4	(1) 0	(1) 0.10	(1) 45	(3) 4.7	7.7/ 6.9†	(1) 533	(1) 55.7
A. P.	Minimum	....	...	....	...	....	..	2.8	...	...	....
	Maximum	....	...	....	...	....	..	10.0	...	...	....
	Mean (1)	22.0	(1) 2+	(1) 7.7	(1) 0	(1) 0.21	(1) 54	(2) 6.4	9.8/ 6.8†	(1) 1,015	(1) 38.4
B. P.	Minimum	25.4	...	....	...	....	..	2.8	...	345	61.6
	Maximum	43.0	...	....	...	....	..	12.1	...	528	82.9
	Mean (9)	30.9	(1) 2+	(1) 16.5	(1) 0	(1) 0.20	(1)116	(6) 6.2	7.5/ 6.9†	(2) 437	(2) 72.3
J. P.	Minimum	20.1	...	....	...	....	..	2.5	...	...	....
	Maximum	29.0	...	....	...	....	..	3.4	...	...	....
	Mean (2)	24.6	(1) 3+	(1) 25.6	(1) 0	(1) 0.27	(1) 35	(2) 3.0	25.5/ 9.9†	(1) 400	(1) 44.8
D. S.	Minimum	19.5	...	....	...	....	..	2.8	...	145	74.2
	Maximum	51.9	...	....	...	....	..	6.5	...	455	115.0
	Mean (6)	35.2	(1) 3+	(1) 44.5	(1) 0	(1) 0.70	(1) 34	(8) 4.6	14.0/ 9.3†	(2) 300	(2) 94.4
A. Z.	Minimum	21.4	...	....	...	....	..	2.1	...	419	42.3
	Maximum	49.3	...	....	...	....	..	9.2	...	605	154.0
	Mean (15)	32.7	(1) 1+	(1) 58.8	(1) 0	(1) 0.90	(1) 31	(6) 3.9	11.0/11.8†	(2) 512	(2) 98.2

* Numbers in parentheses represent the number of determinations performed.
† At the right of the diagonal line are the control figures.

phosphatase values observed in 1 case (A. C.) may be related to his low serum calcium values and roentgenographic evidence of bone rarefaction rather than to hepatic dysfunction. Of the ten determinations of prothrombin time performed, two (J. P. and D. S.) were significantly prolonged. Excretion of sulfobromophthalein was consistently normal in all cases studied. As was noted, several patients with high carotene levels did not show corresponding increases of vitamin A levels in serum. This may be a further indication of impaired hepatic function,

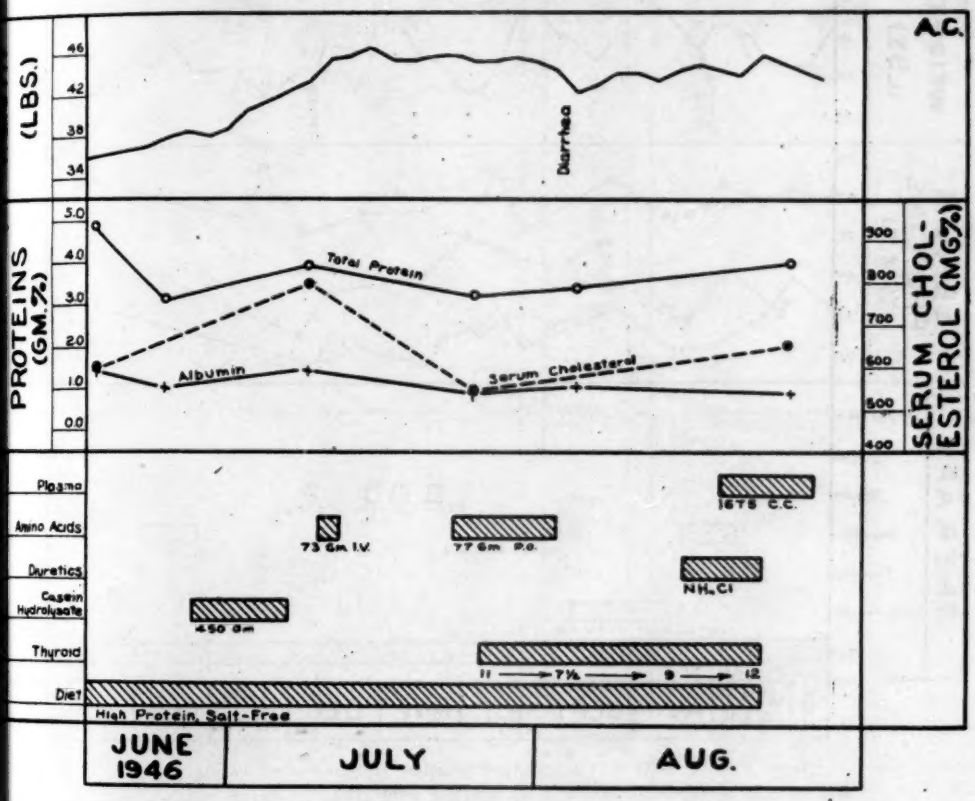

Chart 1 (patient A. C.).—Relation between the course of edema, serum protein and serum cholesterol levels and the therapy employed.

namely the ability to convert carotene into vitamin A. This lack of parallelism between carotene and vitamin A levels was observed in patients receiving thyroid medication as well as in those who did not.

These results indicate that at some time during the course of their illness, all the children showed one or more signs of hepatic dysfunction. In general, the departures from normal were relatively slight. The thymol turbidity test was the only measure of hepatic function showing consistently abnormal values in all patients. While the data do not

warrant attributing a primary or prominent role to disturbed hepatic function in the disease picture of nephrosis, the findings nevertheless are suggestive of some impairment of function of this organ and serve to indicate a possibly fruitful avenue of approach to the problem of nephrosis.

B. Clinical Course and Response to Therapy.—The clinical course, as reflected by the weight curve or degree of edema, the levels of

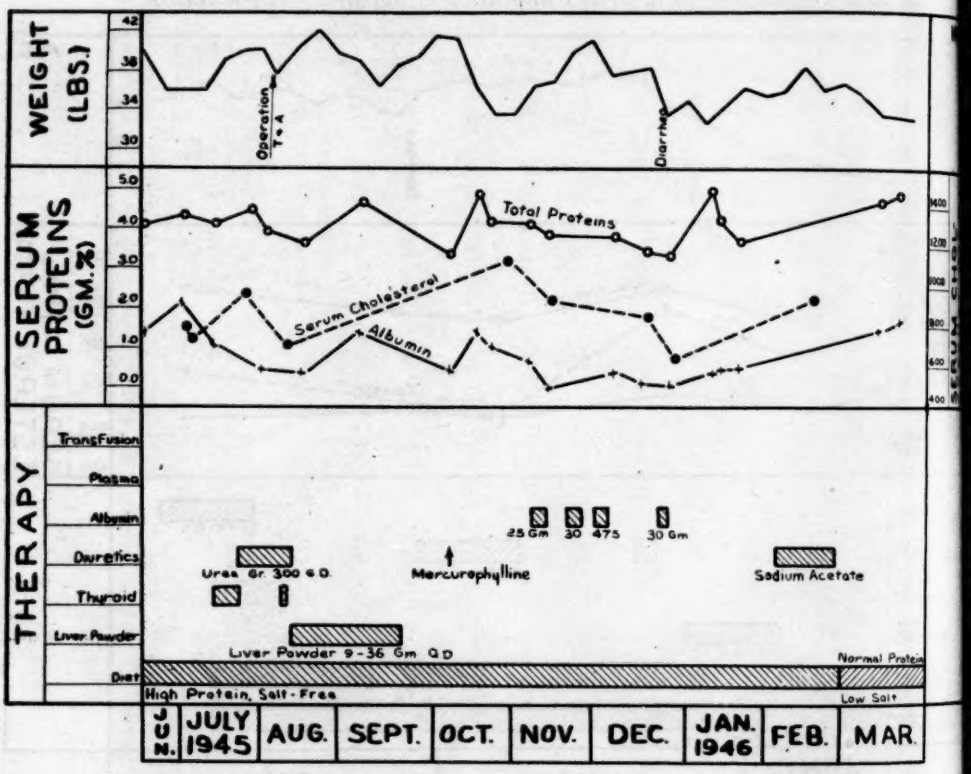

Chart 2 (patient M. G.).—Relation between the course of edema, serum protein and serum cholesterol levels and the therapy employed.

serum protein and serum cholesterol and the therapy employed, are presented graphically in 8 of the 10 cases studied (figs. 1 to 9).

Analysis of the graphic records permits the following generalizations to be drawn with regard to the relationship between serum protein levels and the degree of edema: 1. A rise in total proteins above a level of 4.0 Gm. per hundred cubic centimeters, or in serum albumin above 1.5 Gm. per hundred cubic centimeters, is almost invariably associated with a decrease in edema. 2. Conversely, a fall in total proteins below 4.0 Gm. per hundred cubic centimeters, or in serum albumin below 1.5

Gm. per hundred cubic centimeters, is almost invariably associated with an increase in edema. 3. If the levels of total protein remain below 4.0 Gm., or of serum albumin below 1.5 Gm. per hundred cubic centimeters, there is no correlation between fluctuations in the protein levels and the degree of edema. Indeed, below these levels, edema tends to increase progressively, regardless of fairly large variations in the protein levels. 4. However, loss of edema occasionally occurs with total

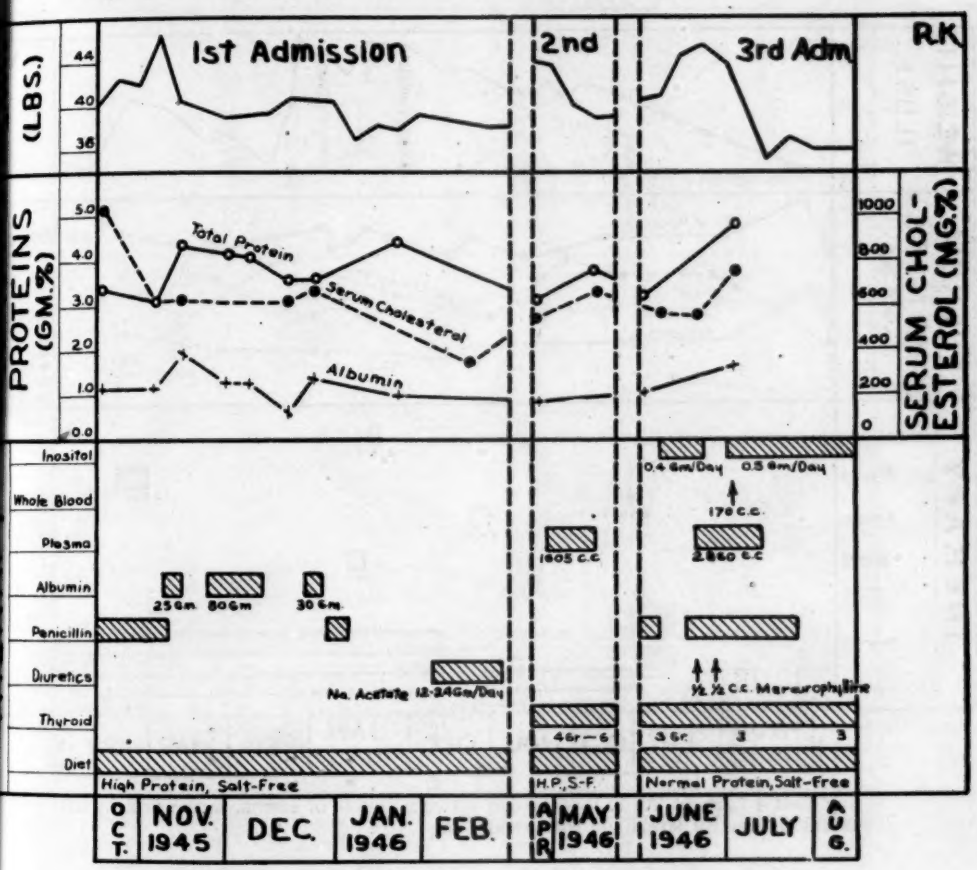

Chart 3 (patient R. K.).—Relation between the course of edema, serum protein and the serum cholesterol levels and the therapy employed.

proteins at lower levels than 4.0 Gm. or serum albumin of 1.5 Gm. per hundred cubic centimeters, in association with certain types of therapy, intercurrent infection or diarrhea.

These observations indicate that there exists a critical level of serum protein, in the neighborhood of 4.0 Gm. per hundred cubic centimeters for total protein and 1.5 Gm. per hundred cubic centimeters for serum albumin, above which variations in the protein level, and hence of the

colloid osmotic pressure of the blood, play a significant role in the course of the edema. It should be noted that this critical level does not imply a threshold below which edema regularly occurs or above which edema is usually absent, as does the level of 5.5 Gm. of total protein and 2.5 Gm. per hundred cubic centimeters of serum albumin given by Peters and Van Slyke.[2] It marks rather the lower limit of a range within which variations in the protein level have a demonstrable effect on the trend of formation of edema or resorption. Below this critical range,

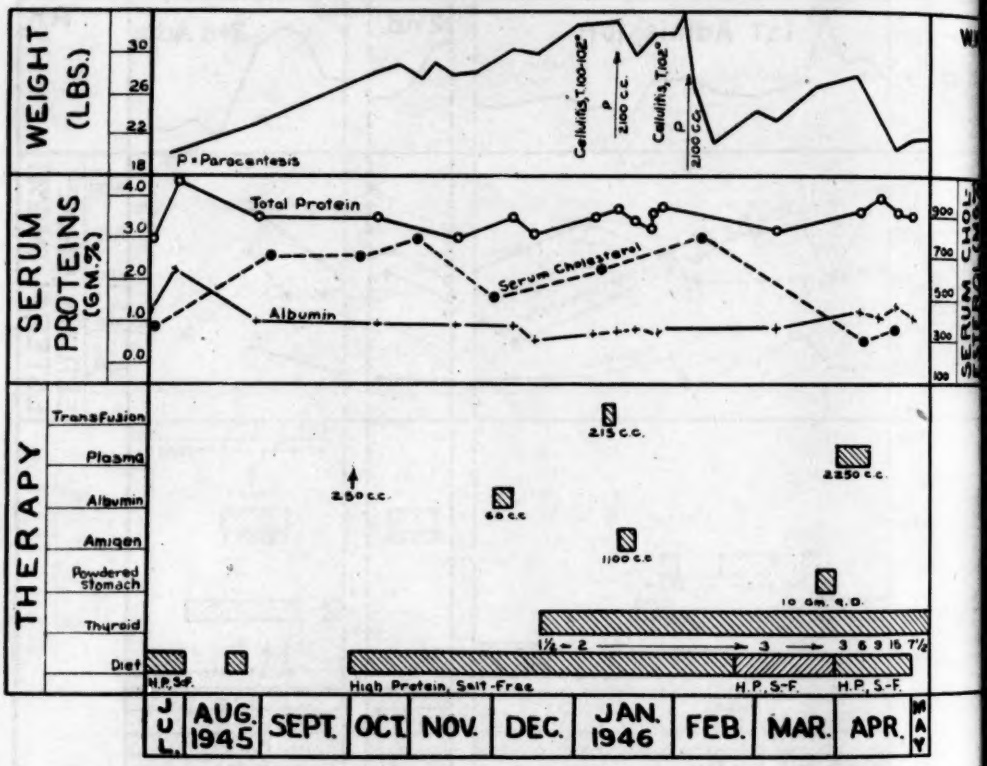

Chart 4 (patient W. K.).—Relation between course of edema, serum protein and serum cholesterol levels and the therapy employed.

factors other than the concentration of plasma protein appear to play the decisive role in determining the degree of edema.

No correlation was observed between the values obtained for serum proteins and serum cholesterol. In accord with the observations of Heymann and Startzman,[31] serum cholesterol was found to vary directly or inversely as the serum proteins with equal frequency. As a con-

31. Heymann, W., and Startzman, V.: Lipemic Nephrosis, J. Pediat. **28**:117. 1946.

comitant observation, no correlation was noted between the serum cholesterol levels and the degree of edema.

The treatment employed consisted primarily of rest, dietary control, parenteral replacement of protein and control of infection. Other measures included the use of thyroid, diuretics, hydragogue cathartics, abdominal paracentesis and various lipotropic agents, liver concentrates, hematinics and vitamins.

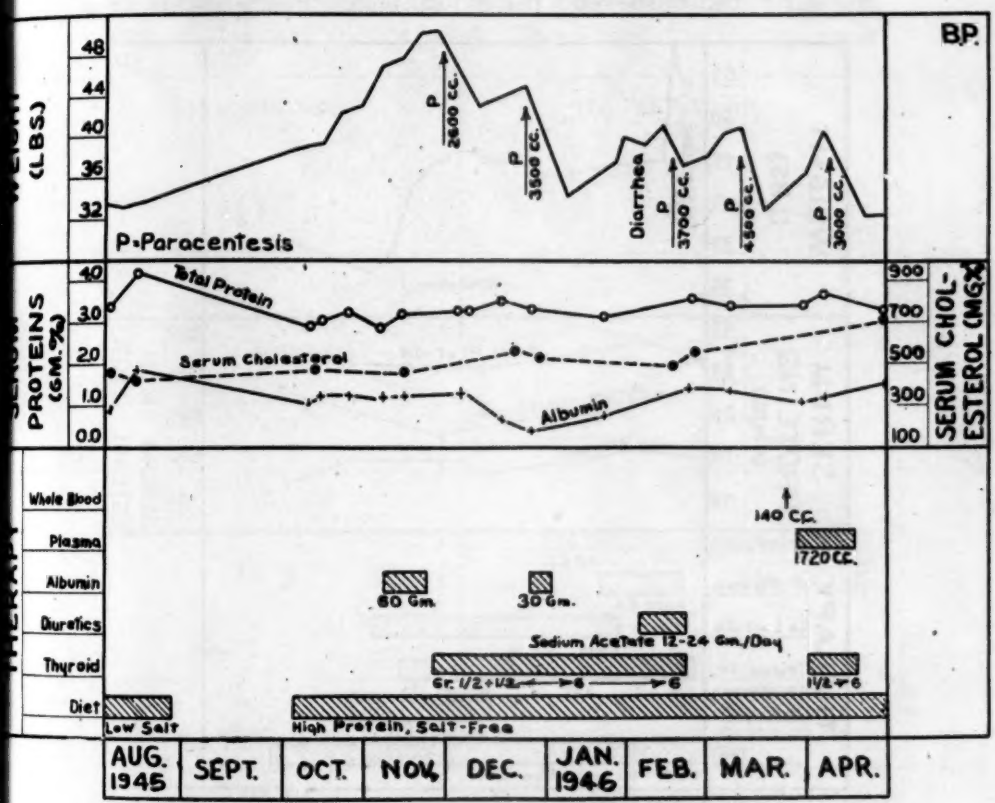

Chart 5 (patient B. P.).—Relation between course of edema, serum protein and serum cholesterol levels and the therapy employed.

1. Diet: All patients received a diet high in protein and salt poor throughout the greater part of their hospital stay, containing 3 to 6 Gm. protein per kilogram of ideal body weight and a maximum of 1.5 Gm. of sodium chloride per day. Normal protein, low protein, and special diets (rice) were used for shorter periods (two to five weeks) in 5 cases, without appreciable difference in therapeutic effect.

2. Parenteral Replacement of Protein: (*a*) Transfusions of whole blood were employed in 6 cases, with some improvement of anemia

but no significant effect on serum proteins, weight curve or general condition.

(*b*) Plasma, usually reconstituted to yield a concentration four times that of normal plasma, was given to 6 patients with inconstant results. Occasionally, the use of plasma was followed by an increase in total proteins and serum albumin, with an accompanying diuresis, as in W. K. (fig. 4). With the administration of 2,250 cc. of plasma in a two week period, this patient showed a rise in total protein from a level of 3.5 to

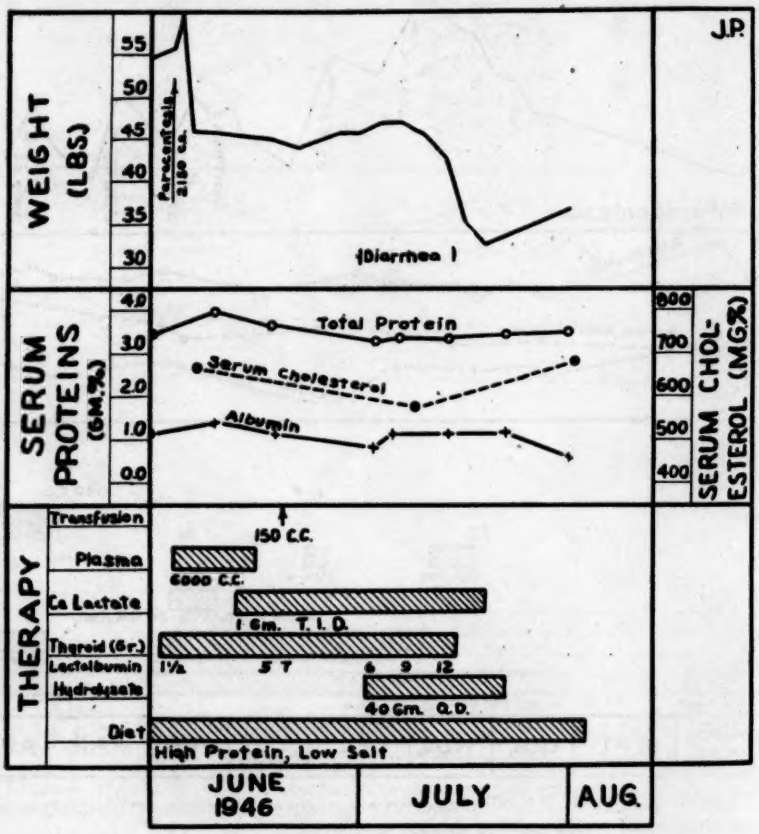

Chart 6 (patient J. P.).—Relation between course of edema, serum protein and serum cholesterol levels and the therapy employed.

4.0 Gm., and of serum albumin from 1.0 to 1.3 Gm. per hundred cubic centimeters. This was associated with a loss in weight of 4 pounds (1.8 Kg.) and subsidence of edema. In other cases, typified by A. Z. (fig. 8), administration of as much as 1,000 cc. of plasma in one week was accompanied by a fall in total proteins and serum albumin and an increase of edema.

(*c*) Salt-poor human serum albumin [32] was employed in 6 cases. Occasionally its use was followed by dramatic improvement in both the clinical and chemical aspects of the disease, as seen in its first trial in A. Z. (fig. 8). However, these effects were inconstant, and this same patient later showed no response to repeated trials of this therapy. In some cases (M. G., fig. 2), there was an actual fall in serum albumin and increase in edema following this therapy.

(*d*) A casein hydrolysate [33] was given intravenously as a 5 per cent solution to 1 patient without effect. The limited trial of this agent

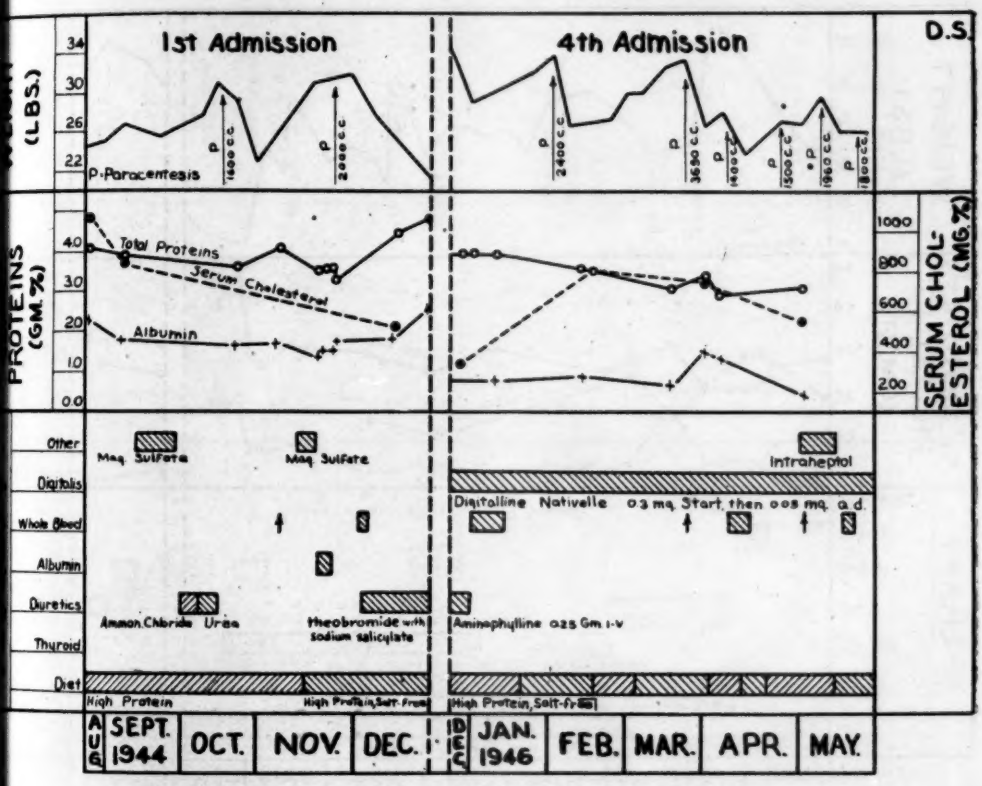

Chart 7 (patient D. S.).—Relation between course of edema, serum protein and serum cholesterol levels and the therapy employed.

does not permit any conclusions to be drawn regarding its possible usefulness.

(*e*) A synthetic amino acid mixture, containing the ten essential amino acids plus aminoacetic acid, in concentrations similar to those

32. This was obtained from Cutter Laboratories, Inc., New York.

33. This product, amigen, was obtained from Mead Johnson & Company, Evansville, Ind.

employed by Bassett and his colleagues,[34] was given intravenously to 1 patient (A. C.). Because of technical difficulties incident to the age of the patient and the severe degree of edema, it was not possible to give as large an amount of the amino acids by this route as might have been desirable. However, the administration of 73 Gm. of amino acids over a three day period was associated with an increase of edema and no change in the serum protein values.

3. Oral Administration of Protein Hydrolysates and Amino Acids: (*a*) A casein hydrolysate [35] was administered orally to 1 patient (A. C.)

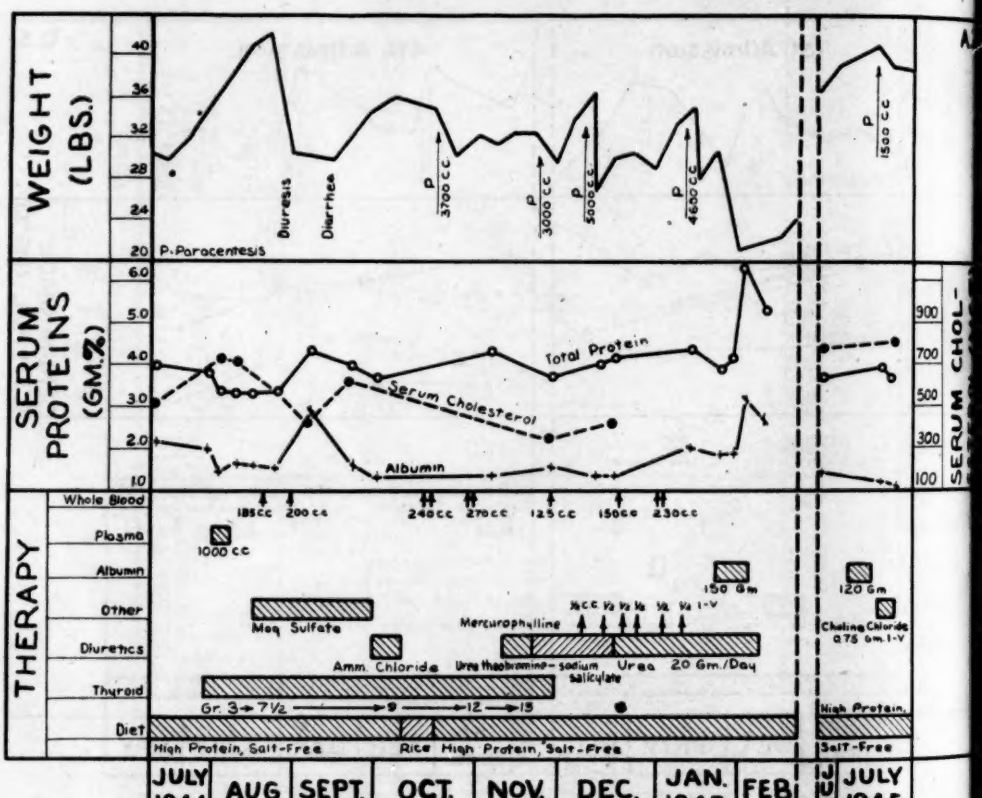

Chart 8 (patient A. Z.).—Relation between course of edema, serum protein and serum cholesterol levels and the therapy employed.

in amounts of 50 Gm. per day over a nine day period. This was associated with a slight rise in total proteins and serum albumin, but accompanied by gain in weight of 4 pounds (1,814 Gm.) and increased edema.

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34. Bassett, S. H.; Woods, R. R.; Shull, F. W., and Madden, S. C.: Parenteral Amino Acids as a Source of Protein in Man, New England J. Med. **230**:106, 1944.

35. This product, protein hydrolysate, was obtained from E. R. Squibb & Sons, New York.

(*b*) A lactalbumin hydrolysate[36] was given by mouth to 2 patients. One (J. P.) showed no change in serum proteins, but lost 13 pounds (5.9 Kg.) of weight in one week, with virtually complete loss of edema, on a dosage of 40 Gm. per day of this hydrolysate. This loss of weight was associated with a rather severe diarrhea rather than a true diuresis. The concomitant administration of 6 to 12 grains (0.4 to 0.75 Gm.) daily of desiccated thyroid renders it difficult to evaluate this therapy.

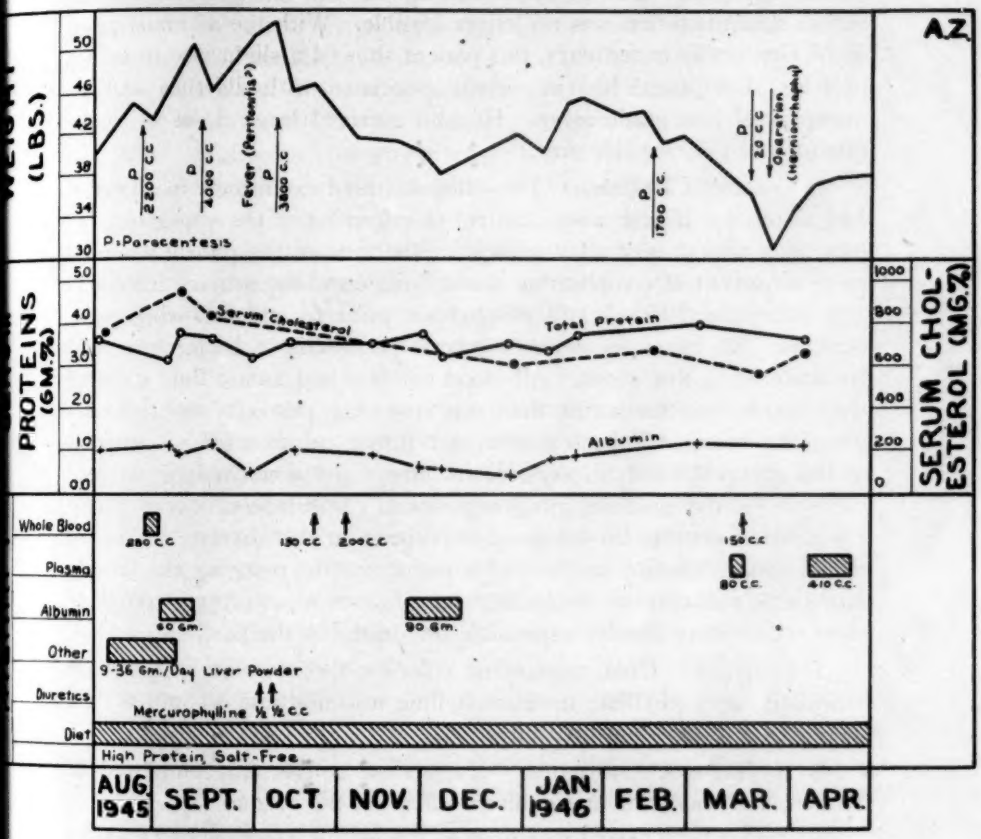

Chart 9 (patient A. Z.).—Relation between course of edema, serum protein and serum cholesterol levels and the therapy employed.

Nitrogen balance studies were carried out during the administration of the lactalbumin hydrolysate and during a control period with the patient on a standard high protein, salt-poor diet. Positive balances were obtained in both instances, though somewhat larger retentions were observed during the control period. It is of interest to note, in

36. This product, "edamin," was obtained from Sheffield Farms Company, Inc., New York.

conformity with the observations of Farr,[37] that nephrotic patients may be in positive nitrogen balance without showing any parallel increase in their serum proteins. Another patient (A. P.) is receiving lactalbumin hydrolysate at present, with a promising clinical response manifested by loss of weight and edema, but it is too early to evaluate this therapy in her case.

(*c*) The synthetic amino acid mixture described in the preceding section was given to A. C. by mouth, mixed with his diet, when intravenous administration was no longer feasible. With the administration of 77 Gm. orally in ten days, this patient showed a slight rise in serum proteins, a 4 pound loss in weight associated with diarrhea and an unexplained low grade fever. He also received large doses of desiccated thyroid during this time.

4. Control of Infection: Penicillin was used extensively in all cases. Indications for its use were: control of infections of the upper respiratory tract almost invariably present at the time of the patient's admission; treatment of complicating pneumonia, cellulitis, urinary infections and unexplained fevers and prophylaxis prior to and following paracenteses. No instances of pneumococcic peritonitis or bacteremia were encountered in this series. All blood cultures and ascitic fluid cultures were sterile, and the ascitic fluid was free from pus cells or organisms on direct smear. Repeated nose and throat cultures for all patients in this group showed Staphylococcus aureus and nonhemolytic streptococci to be the predominating organisms. Pneumococci were rarely reported, in contrast to the usual experience in this disease. It is felt that penicillin therapy has played a major part in reducing the fatality rate in this disease by decreasing the number of infectious complications which were chiefly responsible for deaths in the past.

5. Diuretics: Urea, ammonium chloride, theobromine with sodium salicylate, aminophylline, mercurophylline injection and sodium acetate were found to have but little effect.

6. Hydragogue Cathartics: Magnesium sulfate was employed in 2 cases, and was without significant effect on the edema.

7. Thyroid: Thyroid was used in 7 cases, in doses up to 15 grains (1 Gm.) per day over periods of two to twenty weeks, with no appreciable effect on the edema, serum lipid values or course of the disease. Occasionally, when toxic doses were reached, characterized by tachycardia, irritability and restlessness, the attendant diarrhea may have contributed somewhat to loss of edema.

8. Miscellaneous Substances: Lipotropic agents, including choline, methionine, lecithin, inositol, crude liver extract and vitamin B complex

37. Farr, L. E.: The Significance of Protein Metabolism in the Nephrotic Child. J. Pediat. **17**:734, 1940.

were tried in several cases, without demonstrable effect. However, the difficulty of administering adequate large doses of these substances in palatable form to children has interfered thus far in carrying out therapy over sustained periods, and renders any evaluation of this therapeutic approach premature. Further studies along these lines seem desirable, and such studies are now in progress at this institution. Liver powder was given to 2 patients (M. G. and A. Z.) in doses of 9 to 36 Gm. per day, with some increase in serum protein and decrease of edema in M. G. (fig. 2). All patients received supplements of vitamins A, B complex, C, and D in amounts of two to three times the minimal daily requirement. Ferrous sulfate was given when indicated, but usually had little effect on the secondary anemia encountered in these patients. Calcium lactate was given orally in doses of 3 Gm. per day in some cases, but was without effect on the hypocalcemia.

SUMMARY

The data concerning the chemical composition of the blood, the clinical course, and the response to therapy of 10 children with the nephrotic syndrome, studied over a period of two years, are presented here.

The values obtained for serum proteins and the various protein fractions, serum lipids, nonprotein nitrogen, urea nitrogen, uric acid, calcium, inorganic phosphorus, chloride, and carbon dioxide content of serum were substantially in accord with the values previously reported by other investigators of this disease. Levels of amino acid nitrogen in the plasma were normal or slightly elevated, even during periods of so-called nephrotic crises. Glucose tolerance curves suggested some disturbance in the absorption and utilization of carbohydrates in nephrotic patients. Carotene values were all considerably elevated, in keeping with the lipemia. Vitamin A levels, however, were normal or only slightly elevated.

Hepatomegaly was a frequent clinical finding in these children. Studies of hepatic function were made, including determinations of serum bilirubin, cholesterol partition, cephalin flocculation, thymol turbidity, serum amylase, alkaline phosphatase, prothrombin time, and excretion of sulfobromophthalein. All patients showed one or more signs of impaired hepatic function at some time during the course of their illness. However, the departures from normal were relatively slight, and it is felt that the present data, while suggestive, do not warrant ascribing a primary or prominent role to impaired hepatic function in the disease picture of nephrosis.

The trend of formation or resorption of edema varied inversely with the serum protein levels when the total serum proteins exceeded 4.0 Gm. per hundred cubic centimeters, or serum albumin exceeded 1.5 Gm.

per hundred cubic centimeters. Below these levels, edema tended to increase progressively, regardless of fluctuations in the concentration of protein in the serum. This suggests that other factors than colloid osmotic pressure are primarily operative in determining the course of the edema in this low protein range. No correlation was noted between serum cholesterol and serum protein levels, nor between serum cholesterol levels and the degree of edema.

The most useful therapeutic measures appear to be restriction of salt, parenteral replacement of proteins and control of infection. Penicillin was used exclusively for the latter purpose in this group of patients; it is felt that this drug has been the chief factor in reducing the fatality rate. The evidence regarding the benefits to be obtained from thyroid, diuretics, hydragogue cathartics, etc., is less convincing. Protein hydrolysates and synthetic amino acid mixtures, as well as the various lipotropic agents, may eventually prove to be of value in the treatment of nephrosis. However, the present data are insufficient to allow any conclusions to be drawn as to their efficacy.

Fig. 1.—The patient at 17 months of age. Note (1) the purplish brown teeth; (2) pigmented scars of hydroa vacciniforme prominent on the forehead, and (3) the hypertrichosis, manifested by the thick eyebrows joining in the midline, the long eyelashes and the low frontal hair line.

PORPHYRIA AND PORPHYRINURIA

Report of a Case; Review of Porphyrin Metabolism with a Study of Congenital Porphyria

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AND
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RED URINE, erythrodontia, hydroa aestivale and hirsutism constitute a rare group of symptoms which describe the most striking of the clinical manifestations of congenital porphyria. More important than the consideration of mere rarity, however, is the fundamental significance of this constitutional anomaly as related to a more complete understanding of the normal and pathologic physiology of pigment metabolism. Indeed, the mode and site of the production and degradation of hemoglobin are still obscure, and the story of pigment metabolism, in general, is yet incomplete. Clinical material for the study of respiratory pigments is available so infrequently that each new instance of congenital porphyria, occurring as an inborn error of hemoglobin synthesis, becomes a matter of considerable interest. A typical case of congenital porphyria is, accordingly, reported, with a review of the literature on porphyria and porphyrinuria. The results of the study of this case of congenital porphyria, including isolation of the porphyrin crystals, determination of the extent of their urinary excretion and the effect of liver therapy are also presented.

REPORT OF CASE

The patient, a 17 month old white girl born on May 25, 1944, was admitted to the Children's Memorial Hospital to the service of one of us (S. G.), on her referral to the hospital by Dr. J. O'Neill, of Ottawa, Ill. The infant weighed 9 pounds 5 ounces (4,224 Gm.) at birth and was the product of a normal, full term second pregnancy. Except for red urine passed several hours after birth, the infant appeared normal. The red coloration of the urine persisted, and its intensity was believed to have increased progressively since birth. At 2 months of age a

From the Children's Memorial Hospital (Dr. Dunsky and Dr. Gibson) and the Department of Physiology, Northwestern University Medical School (Dr. Freeman), Chicago.

vesiculobullous eruption developed on the hands, arms and face, some of the lesions being as large as 3 cm. in diameter. Impetigo was suspected. The lesions resisted therapy, however, and were followed by deep pigmented scars. Conjunctivitis was severe, and an irritability simulating that seen in acrodynia (erythredema polyneuropathy) was pronounced. Several of the finger nails were shed, vesicular lesions developing around and under the nails. At 7 months of age the infant cut her first tooth, the left lower central incisor, discolored a purplish brown. All subsequent teeth were similarly discolored. Growth and development were otherwise normal. There was no consanguinity of the parents, who were both well. No similar metabolic disturbance was known to have occurred in either the mother's or the father's family. The patient's sibling had died at 7 weeks of age, of an unknown cause, but with prominent splenomegaly.

Physical examination on her admission to the hospital revealed an afebrile, irritable, well nourished and well developed white female weighing 29 pounds (13,154 Gm.). Pigmented scars in the skin were noted on the forehead, eyelids,

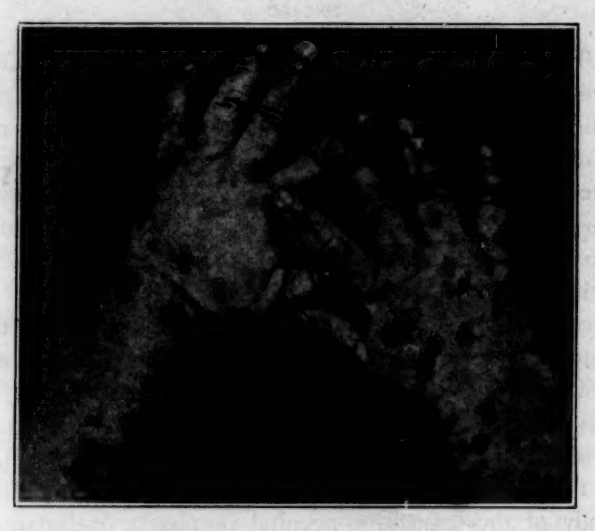

Fig. 2.—The hands and forearms of the patient at 17 months of age. Note (1) the deep bilateral scarring following hydroa vacciniforme; (2) miliary vesicles over the dorsum of right hand, and (3) the vesicle around the nail margin of the right index finger.

cheeks and dorsal surfaces of the hands and forearms. There was little scarring on the lower extremities. Hypertrichosis was pronounced and generalized and made particularly evident by the thick eyebrows joining in the midline, the long eyelashes and the low frontal hair line. Hair was abundant over the upper and lower extremities and present in moderate amount over the back. Several miliary vesicles were noted on the dorsal surface of the right hand and around the nail border of the right ring finger. The surfaces of the nails were irregularly ridged. Sixteen purplish brown teeth were present, displaying zones of varying pigment density. Pigmentation was not as heavy at the biting and gingival margins as at the midportion of the crown, suggesting periods of varying intensity of the metabolic disturbance. The edge of the spleen was palpated 1½ inches (3.8 cm.) below the left costal margin, and the edge of the liver, 1 inch (2.5 cm.) below the right costal margin.

Laboratory Observations.—The blood count revealed the following values: hemoglobin, 9 Gm. per hundred cubic centimeters; red cells, 3,610,000, and white cells 6,700, with a differential count of 48 polymorphonuclear leukocytes and 52 lymphocytes and a platelet count of 75,000. No abnormal or young white blood cells were seen in the peripheral blood, but 2 nucleated red cells per hundred white cells were counted. A reticulocytosis of 7.9 per cent was present. Polychromatophilia was pronounced, and basophilic stippling of the red blood cells was noted. The coagulation time was two minutes and the bleeding time four minutes. The red cell diameter was 7.1 microns; the mean corpuscular volume, 91 cubic microns; the mean corpuscular hemoglobin, 25 micromicrograms; the mean corpuscular hemoglobin concentration, 27 per cent, and the hematocrit reading, 33. Examination of the bone marrow yielded the following values: erythroblasts, 10 per cent; normoblasts, 62 per cent; myelocytes, 2 per cent; metamyelocytes, 1 per cent; stab forms, 2 per cent; segmented polymorphonuclear leukocytes, 1 per cent; lymphocytes, 11 per cent; monocytes, 11 per cent; erythroblast: granulocyte ratio, approximately 6:1 (normal 2:1). The nonprotein nitrogen of the blood was 32 mg.; urea nitrogen, 15 mg.; sugar, 100 mg.; calcium, 11.4 mg.; and phosphorus, 3.8 mg. per hundred cubic centimeters. The phosphatase value was 10.6 Bodansky units and the icterus index, 6. The cephalin flocculation test gave negative results. Cholesterol of the blood measured 256 mg.; cholesterol esters, 185 mg. (72 per cent of total cholesterol); total protein, 7.3 Gm.; albumin, 4.4 Gm., and globulin 2.9 Gm. per hundred cubic centimeters. The fragility test showed hemolysis beginning in a 0.42 per cent solution of sodium chloride and complete in a 0.30 per cent solution for the blood of both the patient and a normal child. Specimens of urine showed a striking red color with a reddish orange fluorescence under the Wood light. A similar fluorescence of the blood serum was seen. The red color of the urine deepened on exposure to sunlight. Repeated analyses of the specimens of urine gave an acid reaction and showed no albumin, sugar, acetone or diacetic acid. The benzidine test gave a negative reaction for blood, and microscopic examination failed to reveal red blood cells, white blood cells or casts. A spectacular reddish orange fluorescence of the teeth was seen on exposure to a Wood light. The Mantoux test (in 1:1,000 dilution) for tuberculosis and the Eagle test for syphilis gave negative results. Roentgenograms of the skull, chest, trunk and upper and lower extremities revealed a normal condition.

A follow-up history obtained one year after the child's admission to the hospital revealed a recrudescence of the vesiculobullous lesions, which were larger and involved the face, scalp, shoulders, arms, forearms and lower extremities up to the knees. Several lesions had appeared on the chest. The skin has become liable to trauma, the child "skinning herself ever so easily." The urine had been constantly red, the intensity of color never lessening even during episodes of fever. Administration of sulfonamide drugs to the patient did not seem to affect her adversely. Hirsutism was more conspicuous. The finger nails had been shed twice during the year, and scarring was more pronounced. The spleen had increased in size, and the presence of anemia was now very apparent. Liver extract was being administered.

Study of Excreted Porphyrins.—A chemical study of the porphyrins involved in the excretion was carried out by one of us (S. F.).

The urine of the patient was reddish brown. The qualitative test for porphobilinogen described by Watson and Schwartz [1] gave negative results. An untreated

1. Watson, C. J., and Schwartz, S.: A Simple Test for Urinary Porphobilinogen, Proc. Soc. Exper. Biol. & Med. **47**:393, 1941.

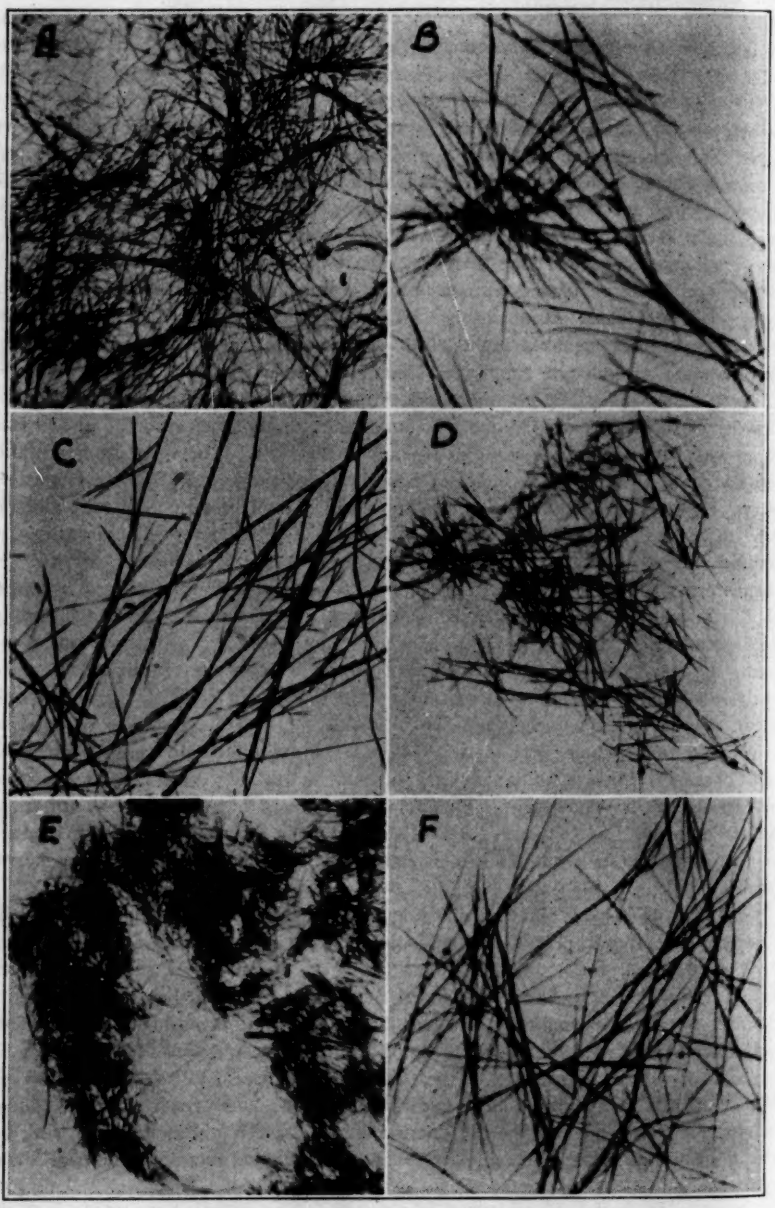

Fig. 3.—*A, B, C, D* show porphyrin crystals of rings 1, 3, 4, 5, respectively, as isolated from the urine (sample B). *E* and *F* show crystals of rings 1 and 5, respectively, as isolated from the urine (sample *A*).

sample of urine at p_H 7.0 had absorption maxima at 580 and 640 millimicrons. When treated with hydrochloric acid, the absorption peaks of the urine shifted to 552 and 595 millimicrons. Absorption of the urinary pigment on calcium phosphate yielded a pink precipitate, which when eluted with acid ethyl alcohol had well defined absorption maxima at 596 and 553 millimicrons. When the precipitate was made alkaline with sodium hydroxide, there were absorption bands at 622, 570, 537 and 510 millimicrons, down past 500 millimicrons, as seen in a Bausch & Lomb spectroscope.

Quantitative estimation of the red fluorescence with the Pfaltz and Bauer fluorophotometer according to the method of Mason and Nesbitt [2] indicated that

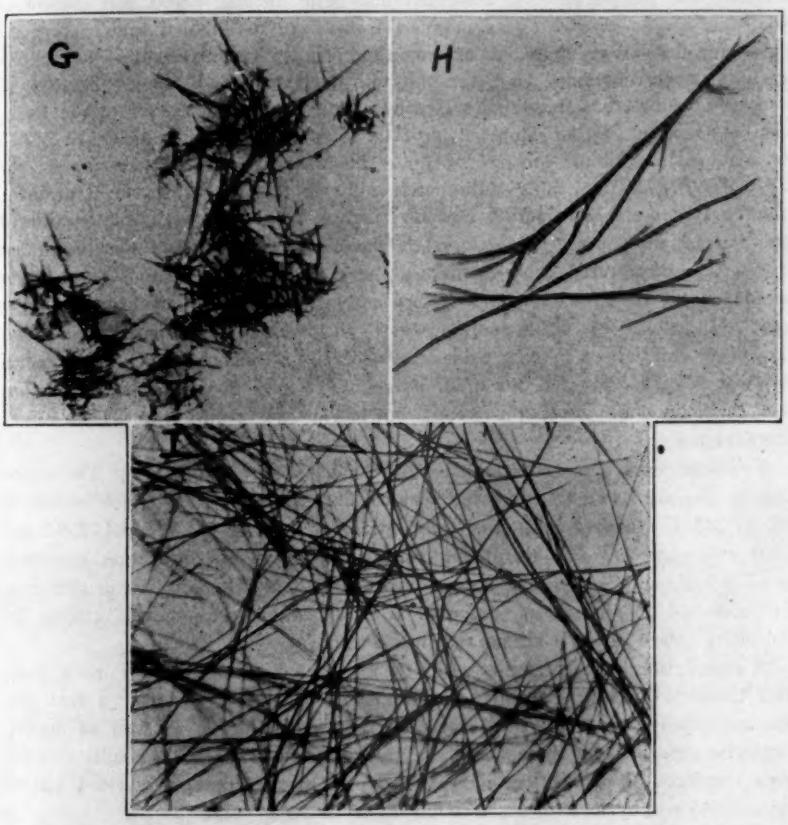

Fig. 4.—*G*, *H* and *I* show porphyrin crystals of rings 2, 3 and 4, respectively, isolated from the feces of sample *B*.

the twenty-four hour excretion of urine contained 0.610 mg. of an ether-soluble substance giving rise to red fluorescence. The standard for this determination was a solution of coproporphyrin.[3] The total red fluorescence of the urine determined against the same standard was equal to 26.6 mg. of coproporphyrin. Assuming

2. Mason, H., and Nesbitt, S.: A Method for the Determination of Coproporphyrin in Urine, J. Biol. Chem. **152**:19, 1944.

3. Dr. Harold Mason provided us with this standard solution of porphyrin.

all red fluorescence to be due to uroporphyrin and coproporphyrin and disregarding the difference in their molecular weight, this amount would indicate a twenty-four hour excretion of uroporphyrin (ether-insoluble porphyrin) equivalent to approximately 26 mg. of coproporphyrin. A few days later, after daily injections of a preparation of the vitamin B complex and liver extract, the twenty-four hour specimen of urine contained 0.183 mg. of ether-soluble porphyrin and a total red fluorescence equal to 9.140 mg. of coproporphyrin.

One twenty-four hour specimen of urine (sample A) was treated according to the method of Schwartz and Watson,[4] and a four day collection of urine and feces (sample B) was fractionated according to the method of Grinstein, Schwartz and Watson[5] for the purification of porphyrins. The melting points and absorption spectrums of the methyl esters in chloroform were determined after rechromatographing the various rings obtained from the primary chromatograms. Crystalline precipitates were obtained from the chloroform eluates of all rings. These were recrystallized before determining their absorption maxima by means of the Beckman spectroscope. From sample A, crystals were obtained which melted at 276 C. (uncorrected), exhibited strong red fluorescence and had absorption maxima at 628.5, 579.0, 542.9 and 507.7 millimicrons. From the second specimen of urine (sample B), a similar fraction (second ring of the primary chromatogram) of long, curved, intertwined reddish crystals was obtained, which had a melting point of 274 C. (uncorrected) and essentially the same absorption bands as the first sample except that the maximum absorption by the longest wavelength of light was 630, instead of 628.5 millimicrons. Just below this ring was another fluorescent ring with a melting point of 209 to 212 C. (uncorrected) and absorption bands at 626, 575, 541 and 505 millimicrons. The next two rings below this had essentially the same absorption maxima but had melting points from 237 to 239 C. (uncorrected).

From the feces, pink and magenta-colored rings were also obtained. The second ring in the primary chromatogram yielded fluorescent crystals which melted at 242 to 245 C. (uncorrected) with absorption maxima of 625.5, 575.4, 539.2 and 505.0 millimicrons. The third ring of the feces had an absorption maximum at 625.9 millimicrons with a melting point of 242 to 246 C. The fourth ring from the feces had an absorption maximum at 632.6 millimicrons melted between 250 and 253 C. and showed a strong red fluorescence.

A comparison of these results with others reported in the literature, particularly with those of Watson, Schwartz and Hawkinson,[6] makes it apparent that uroporphyrin and coproporphyrin I were present in the urine, as well as another porphyrin described by these authors as melting at 208 C. The results obtained from the feces of our patient indicate the presence of coproporphyrin I and an unidentified porphyrin with a somewhat higher melting point.

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4. Schwartz, S., and Watson, C. J.: Isolation of Uroporphyrin from the Feces in Idiopathic Porphyria, Proc. Soc. Exper. Biol. & Med. **47**:390, 1941.

5. Grinstein, M.; Schwartz, S., and Watson, C. J.: Studies of the Porphyrins: I. The Purification of Uroporphyrin I and the Nature of Waldenström's Uroporphyrin, as Isolated from Porphyrin Material, J. Biol. Chem. **157**:323, 1945.

6. Watson, C. J.; Schwartz, S., and Hawkinson, V.: Studies of the Porphyrins: II. Further Studies of the Porphyrins of the Urine, Feces, Bile and Liver in Cases of Porphyria, with Particular Reference to a Waldenström Type Porphyrin Behaving as an Entity on the Tswett Column, J. Biol. Chem. **157**: 345, 1945.

COMMENT

Pigments differing in kind and in their significance may impart to urine grossly similar tints. A red urine is striking and suggests either a substance introduced exogenously as a constituent of food or drugs or a product of endogenous origin. The urine of a patient taking "pyramidon" (aminopyrine U. S. P.) or eating red beets in quantity may have a pink color. The alkaline urine of patients taking phenolphthalein, rhubarb, senna, cascara or santonin may be similarly colored.[7] Amorphous urates, lending a turbidity to acid urine, are precipitated as a pink sediment and are more or less physiologic in the newborn child, being ascribed to a massive destruction of leukocytes in the blood stream at birth.[8] Hematuria, hemoglobinuria and myoglobinuria are endogenous causes of the red coloration of urine. Porphyria, an endogenous anomaly of porphyrin metabolism, is not commonly encountered and consequently is infrequently considered. Porphyria, however, constitutes the most profound of the disturbances of pigment metabolism and is accompanied with the urinary excretion of a galaxy of nonporphyrin substances, including urofiscin, melanin, indole, skatole, leucine, tyrosine and cystine.[9] Porphyrins appear reddish brown in alkaline solution, purple or reddish violet in solutions of mineral acids and dull red in organic acid solutions.[10] They are characterized by an intense reddish fluorescence under ultraviolet light, a maximum fluorescence obtaining with the Wood light.

While comparatively little is known concerning the nature and synthesis of porphyrins in the body, they are recognized as of widespread distribution, constituting as they do, the essential part of the respiratory enzymes present in all living cells. The porphyrins are comparatively stable compounds possessing a nucleus built on four pyrrole rings with substitution groups (side chains) that may differ or be arranged in various isomeric sequences. It is not entirely clear how the body obtains its supply of pyrrole. Porphyrins may be synthesized in vitro from relatively simple chemical substances, including formyl acetone and aminoacetic acid,[11] and by as simple a structure as the yeast cell. With the use of the isotope tracer technic, the participation

7. (*a*) Todd, J. C., and Sanford, A. H.: Clinical Diagnosis by Laboratory Methods, Philadelphia, W. B. Saunders Company, 1944, p. 66. (*b*) French, H.: Index of Differential Diagnosis, ed. 5, Baltimore, William Wood & Company, 1936, p. 893.

8. Brennemann, J.: Practice of Pediatrics, edited by J. McQuarrie, Hagerstown, Md., W. F. Prior Company, Inc., 1945, vol. 1, chap. 42, p. 15.

9. Mason, V. R.; Courville, C. B., and Ziskind, E.: Porphyrins in Human Disease, Medicine **12**:355, 1933.

10. Watson, C. J.: The Porphyrins and Their Relation to Disease: Porphyria, in Christian, H. A.: Oxford Medicine, New York, Oxford University Press, 1938, vol. 4, pt. 2, chap. 9, pp. 1-34.

11. Precursors of the Porphyrins, editorial, J. A. M. A. **130**:32 (Jan. 5) 1946.

of aminoacetic acid in the synthesis of porphyrins in the human subject has been demonstrated.[12] A great number of porphyrins are theoretically possible, but of the four basic etioporphyrins only types I and III are of biologic significance. The most important natural porphyrins are type III protoporphyrin and type I coproporphyrin. The former combines with iron to form heme or hematin-like substances and composes the pigment fraction of hemoglobin, myoglobulin, cytochrome, catalase and peroxidase. Respiratory pigments other than those of a type III configuration do not occur in nature. Free protoporphyrin occurs largely in the young red cells of the bone marrow. Reticulocytes and normoblasts are particularly rich in protoporphyrin, but the substance is not found in appreciable amounts at the erythroblast stage. Formation of protoporphyrin is thus closely associated with formation of hemoglobin. Determination of the erythrocyte protoporphyrin concentration of the blood is of value in the differential diagnosis of the anemias.[13]

Coproporphyrin and uroporphyrin, so named because they were first identified in the feces and urine, respectively,[14] also show a red fluorescence when exposed to ultraviolet light and can be identified by their solubility, melting point of their methyl esters and by their absorption spectrum.[15] The distribution of coproporphyrin in animal and plant life is widespread, and the substance has been identified in potatoes, rutabagas, spinach, bread, milk, beer, fish, grass and leaves.[16] The yeast cell synthesizes coproporphyrin,[17] while production of coproporphyrin and formation of toxin by the diphtheria bacillus are closely correlated.[18] Excreted coproporphyrin is largely, however, an endogenous product. Erythroblasts of the normal embryo regularly contain coproporphyrin,[19] which is also present in the amniotic fluid.[20]

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12. Shemin, D., and Rittenberg, D.: Utilization of Glycine for Synthesis of Porphyrin, J. Biol. Chem. **159**:567, 1945.

13. Watson, C. J.: Some Newer Concepts of the Natural Derivatives of Hemoglobin, Blood **1**:99, 1946.

14. Fischer, H.: Ueber das Uroporphyrin, Ztschr. f. physiol. Chem. **95**:34, 1915.

15. Turner, W. J., and Obermayer, M. E.: Studies on Porphyria, Arch. Dermat. & Syph. **37**:549 (April) 1938.

16. Eldahl, A.: Symptomatology of Acute Porphyria and the Classification of the Porphyrias, Acta med. Scandinav. **97**:527, 1938.

17. Fischer, H., and Fink, H.: Ueber Koproporphyrinsynthesis durch Hefe und ihre Beeinflussing, Ztschr. f. physiol. Chem. **149**:65, 1925.

18. Coulter, C. B., and Stone, F. M.: Occurrence of Porphyrins in Cultures of C. Diphtheriae, J. Gen. Physiol. **14**:583, 1931.

19. Borst, M., and Königsdorffer, H.: Untersuchungen über Porphyrie mit besonderer Berücksichtigung der Porphyria congenita, Leipzig, S. Hirzel, 1929.

20. Gunther, H.: Die Bedeutung der Hämatoporphyrine in Physiologie und Pathologie, Ergebn. d allg. Path. u. path. Anat. **20**:608, 1922.

As injected porphyrins do not traverse the placenta,[21] it is assumed that the embryo synthesizes coproporphyrin, a component of normal meconium. The presence of coproporphyrinuria in small amounts is a physiologic phenomenon. The daily fecal and urinary excretions of endogenous porphyrin amount to from 200 to 400 micrograms in the adult.[22] Coproporphyrin I, generally considered the porphyrin of the normal urine, is present at a daily level of 20 to 50 micrograms, together with traces of uroporphyrin I and coproporphyrin III. Grotepass, however, identified urinary porphyrins as consisting of approximately equal parts of coproporphyrin I and coproporphyrin III.[23]

To understand porphyrin metabolism, it must be appreciated that porphyrins of type I cannot arise from porphyrins of type III except by the splitting of the stable porphyrin molecule and subsequent resynthesis, a process considered most unlikely in vivo.[24] The concomitance of type I and type III isomers has been interpreted, accordingly, as an indication of an independent synthesis of each type, a phenomenon spoken of as the "dualism of porphyrins." Type I porphyrins, therefore, can have no direct connection with hemoglobin, whose prosthetic group, protoporphyrin, as a type III compound, cannot give rise to a type I isomer. Indeed, it has been shown that the degradation of hemoglobin to bilirubin does not normally pass through a porphyrin stage.[25] A constant ratio exists in the body, however, between the formation of type III and that of type I porphyrin compounds, a process hypothetically construed as being controlled by an enzyme system. This system is believed to be selectively catalyzed so that pyrrole precursors, capable of combining to form either type I or type III products, are directed mainly toward the formation of type III compounds, although a side reaction forming some type I isomers occurs.[26] Under normal conditions the ratio of the formation of the type III compounds to that of the type I compounds is 10,000:1.[27] Such a concept, in which the two isomers are visualized as the products

21. Dobriner, K., and Rhoads, C. P.: The Porphyrins in Health and Disease, Physiol. Rev. **20**:416, 1940.

22. Brugsch, J. T.: Untersuchungen des quantitativen Porphyrinstoffwechsels beim gesunden und kranken Menschen, Ztschr. f. d. ges. exper. Med. **95**:471, 1935.

23. Grotepass, W.: Zur Kenntnis der natürlichen Harnporphyrine, Ztschr. f. physiol. Chem. **253**:276, 1938.

24. Fischer, H.: Ueber Porphyrie und ihre Synthesen, Ber. d. deutsch. chem. Gesellsch. **60**:2611, 1927.

25. Lemberg, R.: Transformation of Haemins into Bile Pigments, Biochem. J. **29**:1322, 1935.

26. Rimington, C.: Enzymatic Theory of Erythropoiesis, Compt. rend. d. trav. du lab. Carlsberg, ser. chim. **22**:454, 1938.

27. Watson, C. J.: Porphyrins and Diseases of the Blood, in Symposium of Blood and Blood Forming Organs, Madison, Wis., University of Wisconsin Press, 1939.

of the same chemical process, rather than as the result of an independent synthesis from independent precursors, more adequately explains the observation that coproporphyrin I is excreted at a rate proportional to the formation of type III compounds.

Conditions characterized by an increased production of porphyrin are associated with an increase in fecal and urinary excretion of coproporphyrin I, which serves as an index of hematopoietic activity.[28] An increase in urinary excretion of coproporphyrin I is thus noted after hemorrhage, sickle cell anemia, hemolytic jaundice and pernicious anemia after treatment. A decrease in the excretion obtains in the refractory anemias associated with a hypoplastic marrow.[29] The total quantity of coproporphyrin excreted, as well as the ratio of urinary to fecal excretion, depends, however, not only on the rate of porphyrin production, but also on the physiologic integrity of the liver, which is the main portal of porphyrin excretion. Hepatic dysfunction is accompanied with increased urinary excretion of porphyrin, roughly proportional to the degree of hepatic insufficiency.[30] An increase in urinary excretion of coproporphyrin, usually of type I, obtains in such diseases as catarrhal jaundice, hemolytic jaundice, hepatic cirrhosis and conditions associated with the obstruction of the bile ducts.

The normal process of formation and destruction of respiratory pigments may be disturbed under certain pathologic conditions, resulting in an excretion of type III porphyrins in the urine. Though characterized by the same isomeric configuration as protoporphyrin, coproporphyrin III is apparently formed as a result of a disturbance in hemoglobin formation rather than as a product of hemoglobin degradation.[31] An increased excretion of coproporphyrin III is found associated with aplastic anemia,[32] certain types of hepatic disease,[33]

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28. Dobriner, K.: Excretion of Porphyrins by Dogs, Proc. Soc. Exper. Biol. & Med. **36**:757, 1937. Dobriner, K., and Rhoads, C. P.: Excretion of Coproporphyrin I Following Hemorrhage in Dogs, J. Clin. Investigation **17**:105, 1938. Dobriner, K.; Strain, W. H., and Localio, S. H.: Quantitative Measurement of Coproporphyrin and Total Coproporphyrin I Excretion in Normals, Proc. Soc. Exper. Biol. & Med. **16**:753, 1937.

29. Dobriner, K., and Rhoads, C. P.: Metabolism of Blood Pigments in Pernicious Anemia, J. Clin. Investigation **17**:95, 1938.

30. Nesbitt, S.: Excretion of Coproporphyrin in Hepatic Disease, Arch. Int. Med. **71**:62 (Jan.); 483 (April) 1943.

31. Watson, C. J.: The Relation of the Porphyrins to Erythropoiesis, New York, Science Press Printing Company, 1940.

32. Dobriner, K.; Rhoads, C. P., and Hummel, L. E.: Excretion of Porphyrin in Refractory and Aplastic Anemia, J. Clin. Investigation **17**:125, 1938.

33. Nesbitt.[30] Watson, C. J.: Concerning Naturally Occurring Porphyrins, J. Clin. Investigation **15**:327, 1936. Dobriner, K.: Porphyrin Excretion in Feces in Normal and Pathological Conditions, J. Biol. Chem. **120**:115, 1937; Urinary Porphyrins in Disease, ibid. **113**:1, 1936. Vigilani, E., and Libowitzsky, H.: Ueber Porphyrin im Harn und im Kot, Klin. Wchnschr. **16**:1243, 1943.

pellagra,[34] methyl chloride poisoning [35] and poisoning with heavy metals such as lead, arsenic and mercury.[36] Sulfonamide compounds prompt an abnormal excretion of coproporphyrin III, presumably by blocking the entrance of iron into the porphyrin ring, with a resultant defective synthesis of hemoglobin.[37] The hypochromic anemia of rheumatic fever may have a similar basis, for an increased excretion of type III porphyrins associated with a widespread interference with the various enzyme systems involved in tissue oxidation occurs in rheumatic fever.[38] As the sulfonamide and the aromatic amino compounds are both porphyrinuric and methemoglobinemic in their action,[39] an alternate view has been proposed suggesting that methemoglobin, when once formed, is broken down in part to a type III porphyrin.[37b]

Acute Porphyria.—Porphyrinuria is differentiated from porphyria, the former term merely implying the excretion of porphyrins in excess of normal amounts and the latter denoting a constitutional anomaly regarded as an inborn error of pigment metabolism. An overproduction of porphyrin sufficient to color the urine red occurs almost exclusively in acute and congenital porphyria. Acute porphyria involves the idiopathic disproportionate synthesis of type III porphyrin isomers, particularly uroporphyrin III. The excretion of these porphyrins as a zinc metal complex is characteristic of acute porphyria. The disease is relatively common in Sweden. Waldenström [40] reported 100 cases, while Luthy [41] mentioned an average of 2 new cases reported every

34. Spies, T. D.; Sasaki, Y., and Cross, E.: A Note on the Relationship of Porphyrinuria to Human Pellagra, South. M. J. **31**:483, 1938.

35. Chalmers, J. N. M.; Gillam, A. E., and Kench, J. E.: Porphyrinuria in a Case of Methyl Chloride Poisoning, Lancet **2**:806, 1940.

36. Kurk, R., and Meiklejohn, A. V.: Significance of Porphyrinuria in Lead Poisoning, J. Clin. Investigation **21**:91, 1942. Watson, C. J.: Concerning Naturally Occurring Porphyrins: Urinary Porphyrins in Lead Poisoning as Contrasted with That Excreted Normally and in Other Diseases, ibid. **15**:332, 1936; footnote 27.

37. (a) Rimington, C.: Porphyrinuria Following Sulfonamides, Lancet **1**:770, 1938. (*b*) Rimington, C., and Hemmings, A. W.: Porphyrinuric Action of Drugs Related to Sulphanilamide: Comparison with Reported Toxicity, Therapeutic Efficiency and Causation of Methaemoglobinaemia; Definition of Structure Responsible for Porphyrinuric Action, Biochem. J. **33**:960, 1939.

38. Kapp, E. M., and Coburn, A. F.: Studies on the Excretion of Urinary Porphyrins in Rheumatic Fever, Brit. J. Exper. Path. **17**:255, 1936.

39. Kennedy, A. M., and Ingham, J.: Porphyrinuria in Trinitrotoluene Poisoning, Brit. M. J. **1**:491, 1942. Rimington and Hemmings.[37b]

40. Waldenström, J.: Studien über Porphyrie, Acta med. Scandinav. **82**:1, 1937.

41. Luthy, F.: On the Heredity and Therapy of Porphyria, Klin. Wchnschr. **18**:1034, 1939.

month. Over 250 cases were collected by Chandler and associates[42] up to 1939, with an increasing frequency of reported cases since that time.[43]

The persistence of the metabolic error between attacks and its familial nature suggest that acute porphyria is in essence a chronic congenital process characterized by acute exacerbations and remissions. These may extend over a period ranging from several months to as long as twenty-five years.[44] The disease is transmitted as a mendelian dominant characteristic and is found more commonly in women (in a ratio of 4:1) between the third and fifth decades of life.[40] Acute porphyria may first manifest itself in childhood, however. Rothman[45] described an instance of the disease in a Negro boy 3 years 8 months of age, with a history of repeated attacks of abdominal pain, pain in the legs and difficulty in walking heralding the excretion of red urine and followed by severe polyneuritis with foot drop and wrist drop. Ford[46] cited the history of a girl whose symptoms, starting when she was 8 years of age, consisted of intermittent episodes of abdominal pain, vomiting, constipation, hypertension and porphyria, followed by polyneuritis and muscular atrophy.

Acute porphyria has been divided into toxic and idiopathic forms, the former developing after a long-continued abuse of drugs, frequently the barbiturates, or after lead poisoning. Mason and associates[9] referred to 100 such cases which followed the use of "sulfonal" (sulfonmethane N.F.), "veronal" (barbital U.S.P.) and "trional" (sulfonethylmethane N.F.) taken in daily doses of 1 Gm. for at least a year. Crawford[47] reported a case of acute porphyria in a 4½ year old child with a history of ingestion of lead, intestinal colic and cerebral seizures. Examination revealed flaccid extensor paralysis and a port-wine urine. Gunther[20] expressed the opinion that the drugs were merely precipitating factors in persons with latent porphyria, while Eldahl[16] included infections, exhaustion and anxiety as additional precipitating factors.

42. Chandler, F. G.; Harrison, G. A., and Rimington, C.: Clinical Porphyrinuria, with Report of a Case of the Acute Idiopathic Type, Brit. M. J. **2**:1173, 1939.

43. Nesbitt, S., and Watkins, C. H.: Acute Porphyria, Am. J. M. Sc. **203**:74, 1942. Nesbitt, S.: Acute Porphyria, J. A. M. A. **124**:286 (Jan. 29) 1944. Halpern, R. M., and Copsey, H. C.: Acute Idiopathic Porphyria, M. Clin. North America **30**:385, 1946. Di Fiore, J. A.: Symposium on Problems in Postwar Medicine: Acute Muscular Atrophy with Porphyria; Report of Case, ibid. **30**:397, 1946.

44. Waldenström, J.: Some Observations on Acute Prophyria, Acta med. Scandinav. **83**:281, 1934.

45. Rothman, P. E.: Hematoporphyrinuria, Am. J. Dis. Child. **32**:219 (Aug.) 1926.

46. Ford, F. R.: Diseases of the Nervous System in Infancy, Childhood and Adolescence, ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1944, p. 711.

47. Crawford, H.: A Recent Case of Lead Poisoning Occurring in Brisbane and Associated with Hematoporphyria, M. J. Australia **1**:589, 1933.

Mason and associates[9] assumed that a constitutional inborn error of porphyrin metabolism was not invariably the cause of acute porphyria, but that an exogenous agent might affect persons with a corresponding idiosyncrasy. The idiopathic and toxic forms are, at any rate, clinically and chemically indistinguishable.

The diagnosis of acute porphyria is suggested by the occurrence of gastrointestinal disturbances associated with or followed by neuromuscular or neuropsychiatric symptoms in a patient passing a red urine. As urine may be excreted containing the colorless porphyrinogen, which darkens only slowly on standing and exposure to light or on the addition of an oxidizing agent, the possibility of such a diagnosis may easily be overlooked. Watson's test for porphobilinogen is simple and is said to be pathognomonic of the disease.[1] The abdominal pain is presumably due to a porphyrin effect of tonic contraction of smooth muscle, an effect not abolished by atropine. Abdominal pain is rarely mild; usually it is sudden, violent, colicky, diffuse or localized, occasionally radiating to the chest, back or thighs. It is significant in terms of differentiation from other intra-abdominal conditions that muscular spasm, tenderness or rebound tenderness do not ordinarily obtain.[48]

A laparotomy may be prompted because of a similarity to appendicitis, intestinal obstruction or disease of the gallbladder. Hypertension and tachycardia are typical, while jaundice and a peculiar brownish pigmentation of the skin are not unusual. Changes in the nervous system are outstanding, and may constitute a grave and the only manifestation of an attack. Irregularly distributed paresthesias, paresis and paralysis, occasionally of the Landry type, are noted. While motor involvement of the lower limbs, giving rise to atrophy and contracture, is most common, the brain stem and cranial nerves may also be affected. Respiratory failure due to bulbar palsy is a frequent cause of death. Psychiatric disturbances, including hysteria, hallucinations of vision and hearing and variants of well known neuroses and psychoses, may occur independently of the lower motor neuron lesions. The appearance of neurologic symptoms is followed by death in 50 per cent of the cases.[9] The disease entity may mimic, and so must be differentiated from, hysteria, the Guillain-Barré syndrome, poliomyelitis, familial periodic paralysis, serum paralysis, tic paralysis and periarteritis nodosa.[49]

Congenital Porphyria.—Like most inborn errors of metabolism, congenital porphyria is commoner in the male (ratio 2:1) and is probably transmitted as a mendelian recessive characteristic.[50] Consanguin-

48. Watson, C. J.: Porphyria, South. M. J. **36**:363, 1943.

49. Hoagland, P. I.: Acute Porphyria: Report of Two Cases with Neurologic Manifestations, Proc. Staff Meet., Mayo Clin. **17**:273, 1942.

50. Fourie, P. J., and Rimington, C.: Living Animal Cases of Congenital Porphyria, Nature, London **140**:69, 1937. Garrod, A. C.: Inborn Errors of Metabolism, London, H. Frowde & Howder, 1923. Waldenström.[40]

ity is only occasionally noted, though the occurrence of the disease in two or more siblings in a family has been repeatedly observed. The anomaly is rare, but the cases studied have done much to clarify the problem of porphyrin metabolism. A total of 86 cases were collected up to 1936,[15] and there have been only occasional reports since that time.[51]

As its name connotes, congenital porphyria may manifest itself at birth and has been found even in the fetus. It is a disease entity characterized by cutaneous photosensitivity, particularly in the spring and summer, red brown to purple pigmentation of the teeth and bones, hirsutism and a red urine. All these symptoms may not be evidenced at one time or by one patient. The urine of a patient with congenital porphyria is often red when first excreted, its appearance preceding the cutaneous eruption which follows repeated exposure to bright light. A red urine usually persists once it appears, and contains relatively enormous quantities of type I porphyrins, particularly uroporphyrin I, in contrast to the urine of acute porphyria, in which excretion of the type III isomer predominates. While this type of excretion is the rule, exceptions to it have been reported.[52] It has often been assumed that the type of porphyrins excreted determines the symptoms, type I porphyrins being more photodynamic than type III isomers. Borst and Königsdorffer [19] found that the discoloration of the bone was due to impregnation with uroporphyrin I, which is also present in combination with the cellular protoplasm of the tissues.

It is true that sensitivity to light is rare in persons with acute porphyria, whereas it is usual in patients with congenital porphyria. Hydroa, one of the best examples of a dermatosis caused by light, is common. It is an entity affecting exposed surfaces, heralded by pruritus and erythema and characterized by a vesiculobullous eruption, which is transformed into crusts and pigmented scars. It occurs in one of two types, as the less severe hydroa estivale and as the severer hydroa vacciniforme, characterized by larger, nonumbilicated bullae with scarring propensities. There are approximately 200 cases of hydroa on record, in only 86 of which has porphyria been evidenced.[15] It is thus apparent that, though the tissues of a porphyric patient possess a pigment with photosensitizing properties, the occurrence of hydroa may be independent of a disturbed pigment metabolism and may likewise be absent in cases of congenital porphyria.

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51. Dobriner, K.; Strain, W. H.; Guild, H., and Localio, S. A.: Excretion of Porphyrins in Congenital Porphyria, J. Clin. Investigation **17**:761, 1938.

52. Rimington, C.: Porphyrins of I and III Series in Congenital Porphyria, Nature, London **140**:105, 1937. Fischer, H., and Libowitzsky, H.: Auftreten von Uro- bzw. Koproporphyrin I bei akuter Porphyrie, Ztschr. f. physiol. Chem. **241**:220, 1936. Fischer, H., and Duesberg, R.: Ueber Porphyrine bei klinischer und experimenteller Porphyrie, Arch. f. exper. Path. u. Pharmakol. **166**:95, 1932.

Type I porphyrins may occasionally predominate in case of acute porphyria and yet no photosensitivity be evidenced. Experimentally, failure to reproduce hydroa in porphyric patients by irradiation is the rule; it has been suggested that porphyria is in indirect effect, rather than the cause, of dermal sensitivity. Fourteen cases of epidermolysis bullosa associated with congenital porphyria were collected by Turner and Obermayer, as well as instances of scleroderma, xeroderma pigmentosum, lupus erythematosus, keloid formation and calcification of the skin.[15] The significance of this association is moot, as is that of the occurrence of porphyrinuria in a host of nonrelated dermatoses.[53] Disfigurement, however related to the porphyrins, is ultimately severe in congenital porphyria. Loss of substance of parts of the ears, nose and fingers obtains, with cicatrization and mutilation to such a degree as to mimic leprosy and syringomyelia. The finger nails, at times discolored a reddish purple, may be shed in the summer during an attack of hydroa. Melanosis and an abnormal hair growth, manifested by thick eyebrows, long eyelashes, low hair line and generalized hirsutism, may be seen. Ocular complications may vary from conjunctivitis, iritis and keratitis to chemosis, ulceration and blindness. Anemia and splenomegaly are rarely seen in a child, and their appearance is often delayed until puberty, while hepatomegaly is frequently absent. Their appearance is related to the severity of the porphyria, for the excretion of porphyrin reduces the amount of pyrrole available for synthesis of hemoglobin.

The rarest and most colorful symptoms of congenital porphyria is the purplish brown staining of the bones and teeth when impregnated with uroporphyrin I. Only 8 instances of erythrodontia associated with congenital porphyria have been reported.[54] Uroporphyrin tends to accumulate in the calcifying zones of bone in congenital porphyria but does not affect cartilage, in contrast to the condition in ochronosis, in which black staining is limited to cartilage and fibrous tissue. The teeth may show no obvious discoloration, however, though the bones may be a dark brown. Deep staining of the roots of the teeth may occur, although the visible crown may not be appreciably discolored. Pigmentation of the mucous membrane at the alveolar margin may be seen. Erythrodontia is interrupted as indicating a process that started in utero. Indeed, the formation and calcification of the major portion of the incisors and of one half of the cuspids are prenatal. The first evidence of calcification of the teeth appears in the upper incisors at the fetal age of 4 months, with further calcification in the lateral incisors,

53. Stokes, J. H.; Beerman, H., and Ingraham, N. R.: Photodynamic Effect in Dermatology, Am. J. M. Sc. **203**:608, 1942.

54. Peachey, C. H.; Dobriner, K., and Strain, W.: Hydroa Estivale in Congenital Porphyria, New York State J. Med. **38**:848, 1938. French.[7b]

cuspids and first and second molars of the upper and lower jaws apparent by the sixth month of intrauterine existence.[55]

The etiology of congenital porphyria is obscure and its treatment, accordingly, limited. The disease is interpreted as a persistence of or reversion to the type of bone marrow erythropoiesis normally present in the embryo. The disease may occur in animals, and it has been studied extensively in cattle.[50] In light of Rimington's hypothesis, the failure to convert porphyrin into hemoglobin may be interpreted as a disturbance in enzymatic activity.

Therapy consists in shielding the patient from sunlight by appropriate clothing and by the application of ointments designed to screen out ultraviolet rays.[56] Calcium therapy has been found to diminish porphyrin excretion in the rabbit but has no such effect in the human porphyric patient. The efficacy of liver therapy is yet unsettled.[57]

SUMMARY

An instance of congenital porphyria in a 17 month old girl is reported. The patient's urine contained uroporphyrin I and coproporphyrin I, as well as an unidentified porphyrin whose methyl ester melted at 209 to 212 C. The feces contained coproporphyrin I and another porphyrin with a somewhat higher melting point, but no uroporphyrin I was detected in the feces of this patient. A review of the literature on porphyrin metabolism is included.

3562 Estes Place, Cincinnati (Dr. Dunsky).

Northwestern University Medical School (Dr. Freeman).

104 S. Michigan Boulevard, Chicago (Dr. Gibson).

55. Noyes, F. B.; Schour, I., and Noyes, H. J.: Textbook of Dental Histology and Embryology, Philadelphia, Lea & Febiger, 1938.

56. Ashby, H. T.: Hematoporphyria Congenita, Quart. J. Med. **19**:375, 1926. Luckiesh, M.; Taylor, A. H.; Cole, H. N., and Sollmann, T.: Protective Skin Coating for Prevention of Sunburn, J. A. M. A. **130**:1 (Jan. 5) 1946.

57. Turner and Obermayer.[15] Dobriner and others.[51]

HYPERIMMUNE SERUMS IN TREATMENT OF WHOOPING COUGH

Clinical Results, with Notes on Bacteriologic Studies and Cutaneous Tests

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IN A RECENT publication, Kohn and Fischer[1] outlined the procedures which they considered essential in the treatment of whooping cough based on observations on 3,843 children over the six year period from 1940 to 1945, inclusive. Of these children, 887 were infants under 1 year of age.

In the present communication we wish to discuss a group of 201 patients who, during the previous study, from November 1944 to June 1945, inclusive, received the treatment described in that report and in addition were given either human hyperimmune whooping cough serum or a refined rabbit serum.

Because of the difficulty of establishing a diagnosis of whooping cough before the occurrence of the typical whoop, only a small number of children (2 per cent) were admitted to the hospital before the whoop was first noted; 77 per cent were admitted during the first week of the whoop and 21 per cent later in the course of the disease.

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This study was aided by grants from Ayerst, McKenna and Harrison, Limited, Montreal, Canada; and from the Cutter Laboratories, Berkeley, Calif.

Dr. Raphael Landau, Dr. Milton Levitin and Dr. Matthew H. Linker, resident physicians, and Miss Anny Muller, nurse in charge of the whooping cough ward, assisted in this study.

1. Kohn, J. L., and Fischer, A. E.: The Management of Whooping Cough with Special Reference to Infants, Am. J. Dis. Child. **73**:663 (June) 1947.

The severity of the illness on admission was judged by the history, the nutritional state, the length and frequency of paroxysms, the frequency of emesis and the state of exhaustion. The extent of pulmonary involvement and the degree of cyanosis, if present, were also noted.

We had attempted previously to evaluate the severity of whooping cough by counting the paroxysms and noting the frequency of vomiting over a twenty-four hour period. We found this method to be impracticable and inaccurate, because the nursing personnel, preoccupied with the care of sick infants, could not record every paroxysm. We felt that, since the same group of supervisory nurses and attending physicians had been observing patients with whooping cough for several years, their clinical judgment in evaluating a specific form of therapy would be just as accurate as any other method previously described. Therefore, the nurses and physicians graded the condition of infants who received serum as follows: (1) improved, (2) unchanged and (3) worse. We classified as improved only patients who showed a decided decrease in coughing and vomiting.

It would have been preferable to have given serum to alternate patients, but it was not felt justified to withhold the serum from any seriously ill patient. Therefore, there were no controls for statistical comparison. Kohn and Fischer [1] cited the incidence of whooping cough as reported by the department of health of the city of New York from 1940 to 1946. During that time there were about 5,700 patients yearly, with an average of 45 deaths per year. Thus it was shown, we believe, that the severity of whooping cough in young children in New York city has varied little in the past six years. We felt, therefore, that the course of illness in this study could be compared with that in previous years.

In the present series of 201 children, 43 received a lyophilized human hyperimmune serum; 109 received a concentrated globulin fraction prepared from human hyperimmune serum [2] and 49 received a rabbit serum which was a refined, concentrated globulin fraction obtained from the serum of rabbits who had been given repeated inoculations of a killed culture of Hemophilus pertussis (phase 1). This serum also contained a pertussis endotoxoid.[3]

Three doses of serum were given intramuscularly to each patient, the infants who were desperately ill receiving serum on three successive days and the remainder of the patients receiving serum every second day. Seven patients who showed no improvement were given additional doses of serum. Infants were given (*a*) the lyophilized serum dissolved

2. Human hyperimmune serum was supplied by the Cutter Laboratories, Berkeley, Calif.

3. Rabbit immune serum was supplied by Ayerst, McKenna and Harrison, Ltd., Montreal, Canada.

in 10 cc. of sterile distilled water, which represented 20 cc. of the original serum, or (*b*) 2.5 cc. of concentrated human globulin, which had been extracted from 20 cc. of the original serum or (*c*) 10 cc. of refined rabbit serum. Some of the older children were given larger doses.

Previous experience with rabbit immune serum had convinced us that it was not so effective as the human hyperimmune serum; for this reason, we decided to use only the human serum for our youngest and sickest patients.

As shown in table 1, there were 120 children under 1 year of age. Human serum was given to 79, and 2 others were given rabbit serum. The other 39 infants, who were given no serum, had mild whooping cough.

RESULTS

We shall first consider the clinical course of whooping cough in the children who were given human serum. Since a similar response

TABLE 1.—*Number of Admissions for Whooping Cough and Number of Children Receiving Human and Rabbit Serum*

	Nov. 1944 to June 1945			
Age	Total Admissions	Human Serum	Rabbit Serum	Number of Deaths
0-1 year	120	79	2	1
1-2 years	127	30	7	2
Over 2 years	263	43	40	1
Totals	510	152	49	4

was obtained with both the lyophilized serum and the concentrated human globulin, the results from the use of these serums are considered together.

The subsequent condition of the infants under 1 year of age who received the human serum was considered improved in 70 of 79 patients, or 88.6 per cent (table 2). It can be seen that the apparent response to the serum of patients over 1 year of age was not so striking as that of the younger infants. Improvement was noted in 66.6 per cent of the children over 1 year of age, as compared with 88.6 per cent under 1 year. It is known that in cases of measles, as shown by Stillerman, Marks, and Thalhimer [4] and Karelitz,[5] the age is important in calculating the optimum dose of convalescent serum. It is conceivable, therefore, that greater improvement would have occurred in the condition of these children with whooping cough had larger amounts of serum consistently

4. Stillerman, M.; Marks, H. H., and Thalhimer, W.: Prophylaxis of Measles with Convalescent Serum: Principal Factors Influencing the Results, Am. J. Dis. Child. **67**:1 (Jan.) 1944.

5. Karelitz, S.: Measles Prophylaxis, New York State J. Med. **35**:876 (Sept. 1) 1935.

been given the older patients. We were unable to do this because of the limited amount of serum available.

There was both clinical and roentgenographic evidence of pneumonic involvement in 33 of the 79 infants (44.2 per cent) and in 20 per cent of the children between 1 and 2 years old. In only 1 child, who had no evidence of pneumonic involvement before treatment, did pneumonia develop after administration of the serum was discontinued.

From our progress notes, we can state that a decrease in paroxysms occurred earlier in the course of whooping cough in this study than was noted in previous years. Emesis was less frequent. The nurses stated that during the months the serum was being administered the ward was quieter both day and night. This was especially true of the infants.

The rabbit serum was given to 49 children, of whom only 9 were under 2 years of age. Of this group of 9 children the clinical course

TABLE 2.—*Results of Serum Therapy for Whooping Cough*

Age	Severity of Illness on Admission			Subsequent Condition			
	Mild	Moderate	Severe	Improved	Unchanged	Worse	Died
Human Hyperimmune Serum							
0-6 months	10	10	21	38	2	..	1
6-12 months	14	13	11	32	6	..	..
1-2 years	8	6	16	20	7	1	2
2-3 years	9	4	3	11	5	..	..
Over 3 years	10	13	4	18	8	..	1
Rabbit Serum							
0-1 year	2	..	..	..	2	..	..
1-2 years	4	3	..	1	5	1	..
2-3 years	5	3	1	4	4	1	..
Over 3 years	9	12	10	10	16	5	..

of the disease was considered satisfactory in only 1. Even in the children of the older age group, the course of the illness was not so favorable as in those children who had been given human serum (14 children of the 40 showed improvement). Pneumonic infiltration was noted in 18 per cent of these children. Two of the children without previous evidence of pneumonia had physical signs, confirmed by roentgenograms, after serum treatment was completed.

There were 4 deaths during the period of this study. Each child who died had received human hyperimmune serum. There were 1 death in the group of 79 children under 1 year of age who had received human serum (1.2 per cent), 2 deaths among the 37 children between 1 and 2 years of age and 1 death among children over 3 years of age. The histories of the 4 children who died are given in detail. Postmortem examination was made on 3 of the children.[6]

6. Necropsy material was studied by Dr. Vera Dolgopol and is reported with her permission.

REPORT OF FOUR CASES

CASE 1.—L. T., a 2 month old girl, was admitted Jan. 24, 1945, with a history of having had a cough for two weeks and vomiting for one week. She had a low grade fever. The child became extremely cyanotic during paroxysms and was distressed by a profuse tracheal mucous secretion. There were a few rales at the bases of both lungs. Roentgenograms of the chest showed several scattered, small infiltrations throughout both lungs. On the second day in the hospital, after a paroxysm, the child stopped breathing and was revived by the use of suction and artificial respiration. She was given dextrose in isotonic solution of sodium chloride intravenously and subcutaneously, as well as large doses of penicillin. She seemed to improve somewhat for a few days, but on the twenty-first day after her admission artificial respiration again became necessary and during one such episode she could not be revived. During this entire period the child was kept in an oxygen tent. She received nine injectins of the concentrated globulin fraction prepared from human hyperimmune serum and two injections of the lyophilized human hyperimmune serum.

Necropsy showed that the heart was normal. Both lungs showed extensive consolidation; only the apexes were air containing. On section, the consolidated areas were deep red; no pus could be expressed, and there was gross evidence of atelectasis and pneumonic consolidation. Bacteriologic examination of both lungs yielded H. pertussis in pure culture. The brain was not examined. The other organs showed no gross abnormality.

Microscopic examination of the lungs showed that some of the alveoli contained exudate and that others were collapsed. The lining of some of the alveoli contained large cells with inclusion bodies. A number of the terminal bronchi were collapsed. In the spleen the lymphoid follicles were extremely depleted. The kidneys showed albuminous degeneration of the tubular epithelium.

CASE 2.—G. P., a 20 month old boy, was admitted on Dec. 31, 1944, with a history of cough and fever of one week's duration. The cough had been paroxysmal for several days. On admission the child's general condition was fair. Respiration was rapid. The temperature was 101 F. for the first three days. The child was placed in an oxygen tent and seemed much improved. He was given sulfadiazine and two injections of human hyperimmune lyophile serum. H. pertussis was recovered from a nasopharyngeal swab taken soon after his admission. On the fifth day in the hospital, while being fed, he had a short convulsion, stopped breathing and could not be revived.

Necropsy revealed no gross abnormality in the heart. There was no evidence of aspiration of food into the tracheobronchial tree. The pleural cavities contained no fluid. The anterior surfaces of the lungs were pink and fluffy. Both posterior surfaces were purplish. The lower part of the middle lobe and the posterior portion of the upper lobe of the right lung were firm on palpation. The left lung was similarly consolidated. The cut surface was dry and presented a mottled appearance of yellowish, irregular areas surrounded by red zones, from which minute droplets of pus could be expressed. The anterior portion of the superior lobe of both lungs and a small portion of the middle lobe of the right lung contained air. The brain was moderately congested and edematous, and there was congestion of the white matter.

Microscopic examination of the heart showed fragmentation of some of the fibers of the ventricles. The interstitial tissue of the myocardium was edematous.

The lungs showed large areas of consolidation, which followed a lobular pattern. Many bronchi contained large plugs of mucoid material. In some bronchi within atelectatic areas, fibrous material was present in the lumen. Large groups of cells in the hepatic parenchyma showed the finely vacuolated appearance characteristic of glycogen deposits. The sinusoids in some parts of the liver were wide and contained a considerable number of nucleated cells of lymphoid and myelogenous origin. A few very wide sinusoids contained occasional eosinophilic myelocytes, which suggested local extramedullary myelopoiesis. In other areas the wide sinusoids were filled with red blood cells.

The malpighian corpuscles of the spleen had been completely depleted of lymphocytes, which were replaced by epithelioid reticulum cells. There was no congestion of the splenic pulp.

The lymphoid follicles of the lymph nodes were depleted and showed replacement with epithelioid reticulum cells. The nodes were heavily congested and edematous.

The meninges showed much congestion. All portions of the brain showed congestion of the veins and capillaries. A number of veins in the cortex of the motor region and in the basal ganglions contained plugs consisting of fibrin, lymphocytes and neutrophils.

CASE 3.—T. A., a 17 month old boy, was admitted on Nov. 21, 1944. The child was known to have had a congenitally deformed heart with cyanosis since birth. He had been exposed to whooping cough by several children in the family and had had a paroxysmal cough for several days.

Physical examination showed a poorly developed child with generalized cyanosis. The heart was enlarged, and rough systolic and diastolic murmurs were heard over the entire precordium. Scattered rales were audible throughout both lungs. The patient was immediately placed in an oxygen tent and given sulfadiazine and hyperimmune pertussis serum. He died within twenty-four hours after admission.

At necropsy the heart showed many deformities. The ductus arteriosus and the foramen ovale were open. There was a large defect in the intraventricular septum and many valvular deformities were present. The lungs showed scattered areas of pneumonic consolidation and atelectasis throughout. On microscopic examination the striations of the myocardium were barely visible. At other places the muscle fibers had been replaced by connective tissue. Examination of the lungs showed areas of consolidation and of atelectasis. There was congestion of the bronchial walls. The spleen and the lymphoid follicles were small and showed lymphoblastic cells.

CASE 4.—E. L., a 4 year old girl, was admitted on Feb. 6, 1945, with a history of a paroxysmal cough for three weeks. Three days before admission the child became severely ill. On admission her general condition was poor. She was cyanotic and dyspneic. Physical examination revealed signs of consolidation over the entire right lung, which was confirmed roentgenographically. The day after admission the child began to have convulsions, which recurred frequently in spite of her being in an oxygen tent. She was given four injections of human hyperimmune globulin serum. She was also given large doses of penicillin, plasma, whole blood and dextrose solution intravenously. The temperature remained between 102 and 104 F. The child died in a stupor six days after admission. Permission for necropsy was not obtained.

BACTERIOLOGIC STUDIES

During the period of this investigation, an attempt was made to ascertain whether the giving of serum had any effect on the persistence of H. pertussis in the nasopharynx. Cultures were obtained from the nasopharynx by the method described by Brooks, Bradford and Barry.[7] Three cultures were obtained on nearly every patient: one, on admission; the second, forty-eight hours after the last injection of serum; the third, just before discharge from the hospital. All culture material was plated and examined in the manner described by Bullowa, Buxbaum and Scheinblum.[8] Although Hemophilus parapertussis was searched for, it was not found in the series studied during the period of serum therapy. It is interesting to note that the organism had been grown from cultures of 6 hospital patients in the previous year.

As shown in table 3, the cultures were persistently negative for H. pertussis for 8 of the 28 patients who received no serum. Of the 20

TABLE 3.—*Relation of Administration of Serum to Persistence of Hemophilus Pertussis*

Serum Administered	Total No. of Children Treated	Presence of Organism in Culture			
		Negative Throughout Treatment	Positive Before Administration of Serum	Negative on Discharge	Positive on Discharge
None	28	8	20	16	4
Human	64	17	47	21	26
Rabbit	36	9	27	12	10*

* No cultures were made for 5 patients on discharge.

patients whose cultures were positive, 4 still showed the organisms on discharge, eight to twenty-one days after the first whoop was noted. For the remaining 16 patients cultures became negative from seven to eighteen days after the onset of whooping.

Of the 64 patients who received the human lyophilized serum or human globulin concentrate, 17 had persistently negative cultures. Twenty-one had negative cultures from one to three weeks after the patient received the last injection of serum. The cultures of 26 patients still yielded the organism on discharge from the hospital, which in some instances was as long as four weeks after the appearance of the whoop.

7. Brooks, R.; Bradford, W. L., and Barry, G. P.: The Method of Nasopharyngeal Cultures in the Diagnosis of Whooping Cough, J. A. M. A. **120**:883 (Nov. 21) 1942.

8. Bullowa, J. G. M.; Buxbaum, L., and Scheinblum, I. E.: Pertussis-Bacteriologic and Agglutination Studies, J. Pediat. **25**:299 (Oct.) 1944.

Cultures were persistently negative for H. pertussis for 9 of a group of 36 patients who received rabbit serum. The cultures of 12 patients which were positive became negative before the time of discharge, and 10 still had positive cultures on discharge. It is evident that the giving of serum had no effect on the persistence of H. pertussis in the nasopharynx.

CUTANEOUS TESTS

Weichsel, Rubin, Cohen and Lapin,[9] utilizing pertussis toxin, showed that in a group of 90 patients, 69 had a positive cutaneous reaction some time during the course of whooping cough. Of a control group of 367 children with a negative history of pertussis, only 18.5 per cent gave a positive reaction. The investigators considered their results uncertain.

Strean,[10] Strean and Grant,[11] and Strean, Lapointe and Dechene[12] published the results of a series of intradermal tests in which a pertussis endotoxoid was used in order to determine immunity in whooping cough.

TABLE 4.—*Results of Cutaneous Tests (Strean Endotoxoid)*

Serum Administered	No. of Children Tested	Number Tested on Admission			Number Tested 48 Hr. After Third Serum Injection			Number Tested Before Discharge		
		Neg.	Doubtful	Pos.	Neg.	Doubtful	Pos.	Neg.	Doubtful	Pos.
None	33	10	6	17	..	..	..	5	7	21
Human	44	10	13	10	13	10	21	4	10	26
Rabbit	39	5	10	17	14	8	21	4	4	23
Totals	116	25	29	44	27	18	42	13	21	70

They expressed the opinion that the test was reliable when the history was doubtful or the cough atypical.

Dr. Strean furnished some of his test material for our use. The dose which we used was 0.1 cc. of a 1 : 600 dilution, which was equivalent to 1/20 minimum lethal dose for mice. Most of the patients were tested three times: (1) on admission to the hospital, (2) forty-eight hours after serum treatment was completed and (3) just before discharge. Of 116 children, 98 were tested on admission; 87, forty-eight hours after

9. Weichsel, M.; Rubin, H.; Cohen, P., and Lapin, J.: Intracutaneous Tests with Pertussis Toxin and Complement Fixation Tests in Whooping Cough, Am. J. Dis. Child. **60**:862 (Oct.) 1940.

10. Strean, L. P.: A Skin Test for Susceptibility to Pertussis, Canad. M. A. J. **42**:525 (June) 1940.

11. Strean, L. P., and Grant, G. A.: The Preparation and Properties of Haemophilus Pertussis Endotoxin, Canad. M. A. J. **43**:528 (Dec.) 1940.

12. Strean, L. P.; Lapointe, D., and Dechene, E.: Clinical Studies in Immunity to Pertussis with the Use of Pertussis Skin Testing Toxin and Antiendotoxin, Canad. M. A. J. **45**:325 (Oct.) 1941.

completion of the serum therapy, and 104, before discharge from the hospital (table 4). It was felt that in testing children there would be enough antibodies in the circulation forty-eight hours after the last injection to neutralize the intracutaneously injected endotoxoid. The patients who did not receive serum therapy were tested only on admission and before discharge.

Three types of endotoxoid material were used: (1) a dried form dissolved in albumin solution, (2) a second dried form dissolved in saline solution and (3) a liquid form, in albumin solution. All three types of test material gave the same type of reaction. Therefore, the results were grouped together. The tests that were read twenty-four hours after injection were considered negative when there was no local reaction, doubtful when there was redness but no induration, and positive when there was redness and induration at least 1 cm. in diameter.

Of the 98 children tested during the first week of paroxysmal cough, 44.9 per cent had a positive reaction to the endotoxoid, 25.5 per cent had a negative reaction and in 29.6 per cent the reaction was doubtful. No appreciable change was noted in the 87 children tested forty-eight hours after serum therapy. During the third week of the whoop, when the presence of some immunity had been demonstrated by means of agglutination tests, 67.3 per cent of the children had a definitely positive reaction, as compared with 12.5 per cent, who had a negative reaction. In 20.2 per cent the reaction was doubtful. All those children who showed positive reactions on admission continued to do so. Thirteen children who had had a negative reaction to the test on admission still showed a negative reaction on discharge. On the basis of this evidence, the Strean test does not seem to be a true index of immunity in whooping cough.

COMMENT AND SUMMARY

Felton [13] recently reviewed the use of the lyophilized type of hyperimmune serum. The report particularly emphasized the results obtained by McGuinness, Bradford and Armstrong [14]; McGuinness, Armstrong and Felton,[15] and Scheinblum and Bullowa [16] in 565 children, of whom

13. Felton, H. M.: The Status of Passive Immunization and Treatment in Pertussis by the Use of Human Hyperimmune Serum, J. A. M. A. **128**:26 (May 5) 1945.

14. McGuinness, A. C.; Bradford, W. L., and Armstrong, J. G.: The Production and Use of Hyperimmune Human Whooping Cough Serum, J. Pediat. **16**:21 (Jan.) 1940.

15. McGuinness, A. C.; Armstrong, J. G., and Felton, H. M.: Hyperimmune Whooping Cough Serum: Further Studies, J. Pediat. **24**:249 (March) 1944.

16. Scheinblum, I. E., and Bullowa, J. G. M.: The Treatment of Pertussis with Lyophile Hyperimmune Human Pertussis Serum, J. Pediat. **25**:49 (July) 1944.

459 were under 1 year of age. The mortality rate of the latter group was 1.8 per cent. Felton [13] commented that when serum was used there was a dramatic reduction in the fatality rate, which was said to have been as high as 25 per cent for infants less than 6 months old. Our past experience at the Willard Parker Hospital could not have justified the expectation of such a high mortality rate. During a five year period the death rate for the infants less than 1 year of age under our observation who did not receive serum was only 4.9 to 6.7 per cent. Our data demonstrated that the mortality rate for the infants under 1 year who received serum was lower than that for infants who did not receive serum. There was 1 death in 79 children under 1 year of age, a rate of 1.2 per cent, and 2 deaths in 37 children between 1 and 2 years of age. One of the latter children had had a congenital heart deformity and had been cyanotic since birth.

In a previous paper two of us (J. L. K. and A. E. F.)[1] described the procedures which we believe had appreciably reduced the mortality and lessened the severity of the course of whooping cough, especially in infants. However, one cannot use mortality rate alone as a criterion in evaluating a method of treatment of this disease.. Our case records illustrate how difficult is the evaluation of a single therapeutic measure for an illness such as whooping cough, which has such a variable course. Certainly, there was no dramatic change in our patients, such as has occurred in some of the other acute infectious diseases for which the new antibiotics are employed. Penicillin was used for only a few of our patients, including 2 who died. Therefore, this antibiotic was not a factor in the lowered death rate of the serum-treated patients.

We believe that the addition of administration of human hyperimmune serum to the procedures described by us in our previous paper shortened the period of severe paroxysms and resulted in less emesis. The infants were able to get more rest and to retain more food. The younger children responded more favorably to the therapy than did the older ones. Perhaps this can be explained by the fact that the illness in the older children is less severe and that the therapeutic effect of serum is therefore. less striking. However, the difference in response may have been due to the insufficient dose given the older age group.

Beaudet [17] reported on a series of patients treated with hyperimmune rabbit serum. He expressed the opinion that the treatment had had a beneficial effect on the course of the illness. Our impression was that human serum was far more effective than rabbit serum.

The disappearance of H. pertussis from the nasopharynx bore no relation to the clinical course of the illness and the persistence of the organisms was not affected by the administration of serum.

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17. Beaudet, J. P.: Sérothérapie de la coqueluche, Union méd. du Canada **73**: 137 (Feb.) 1944.

Cutaneous tests made with pertussis endotoxoid (Strean) gave uncertain results.

CONCLUSIONS

Our results suggest that human hyperimmune serum or globulin should be used in treatment of all infants who are seriously ill with whooping cough. The lowered mortality rate in the infants treated with serum in this series may have been due not only to administration of the serum but also to the improved medical procedures and better nursing care.

50 West Ninety-Sixth Street, New York.

ABSTRACT OF DISCUSSION

This discussion is the abstract of a discussion on a paper read before the Section on Pediatrics at the Ninety-Sixth Annual Session of the American Medical Association, Atlantic City, N. J., June 11, 1947. That paper was a résumé of the paper by Dr. Kohn and Dr. Fischer in the June issue of the AMERICAN JOURNAL OF DISEASES OF CHILDREN, page 663, and the present paper.

DR. RUTH G. ALEMAN, New Orleans: Nursing care is most important, and the efficacy of the measures the authors have outlined is well established. In addition to the therapeutic measures described, ether in oil administered by rectal instillation or hypodermically is of benefit in cases of extreme severity.

An interesting phase in the study of whooping cough is the decided increase in the morbidity rate in New Orleans this year. From the beginning of 1947 through May 24 there have been more new cases reported than during the whole of 1946, and almost as many as the total for 1945. I have no doubt that this is because during the first two war years young mothers, in following their husbands from camp to camp, or carrying the burden of parenthood alone, overlooked the importance of having their babies immunized. These nonimmune children, now in school, not only are having whooping cough but are spreading it among young infants. Fortunately, there have been no deaths so far, but the serious illness of an infant in the first few weeks or months is a deplorable handicap with which to start life. This community did not safeguard the health of its children as wisely as did Evanston, Ill., where Dr. Louis Sauer, with the cooperation of local health authorities, established beyond question that whooping cough can be completely eradicated.

At this centennial meeting of the Association, it is particularly appropriate that we take stock, as it were, of our medicine chest. Before the founding of the American Medical Association, a hundred years ago, as well as since, countless remedies had been tried for whooping cough. Today, the entire treatment has been reversed. For blood letting, present day physicians have substituted blood transfusions and the administration of plasma. Instead of starving the patient, we select a nourishing diet rich in vitamins. Instead of dehydrating with purging and vomiting, we supply sufficient liquid.

The reduction in the mortality of whooping cough has been facilitated during the last few years by better nursing, by a better understanding of feeding, by wider use of blood transfusions and by the advent of lyophil, vaccines, serums, the sulfonamide drugs, penicillin and streptomycin.

While we apply these and other therapeutic measures, let us not overlook the well established fact that whooping cough can be prevented. With this knowledge, we begin the second century of the Association most auspiciously; if we fail in its

application, we shall have fallen short of our professional ideals. Medical research has isolated the bacillus of pertussis and has prepared a preventive vaccine which, when properly administered, provides adequate immunity. If all infants are immunized at 6 months of age and given "booster" doses at later intervals, there will be no whooping cough with which to infect babies under 6 months of age. What has been done in Evanston can be done elsewhere. Let us face the facts. Every death from whooping cough is a needless sacrifice of human life, and every case of this disease is a condemnation of modern civilization.

DR. L. NELLES SILVERTHORNE, Toronto, Canada: In this discussion, I shall refer to the various procedures the authors have recommended in the management of whooping cough, with comments and comparisons with the methods of treatment which my colleagues and I use at the Hospital for Sick Children.

1. Experienced and continuous nursing is essential, as babies often die in one of the paroxysmal attacks. They often choke as a result of the thick, tenacious mucus, which a young infant is not able to cough up. It is obvious that a nurse in constant attendance can do much to save the life of such a patient.

2. Oxygen is also essential in the treatment of any infant who is "blue," who has pneumonia, or who is having severe paroxysmal attacks. Our practice has been to place any infant with anoxia during whooping cough in an oxygen box delivering air containing 40 to 60 per cent oxygen. Oxygen gives relief and has a sedative effect. Many institutions assume that sufficient oxygen will be provided by an oxygen tent. I believe that if many of the tents or boxes were tested for the percentage of oxygen delivered some startling facts would come to light. In our hospital in past years, many of our tents and boxes have delivered less than 40 per cent oxygen, as shown by our tests. In my opinion, we should prescribe oxygen to be given at a concentration of over 40 per cent at least. Lower values than this are likely to be useless and wasteful. Oxygen well administered is definitely indicated in all severe cases of whooping cough.

3. The aspiration of mucus from the throat, larynx and trachea of the desperately ill infant is life saving. We have an electrically driven aspiration apparatus, as indicated by Dr. Kohn and Dr. Fischer, which is kept constantly available in the patient's cubicle. When the patient goes into a state of collapse as a result of choking on mucus, the secretions are aspirated, and the baby is given manual resuscitation. I agree with the authors that this procedure has meant the difference between life and death.

4. Administration of cough mixtures to infants, in my opinion, should be condemned. I believe they stimulate the production of mucus and consequent choking. Any irritant of this type causes the whole paroxysmal act to recur at each administration of the medicine. Sulfadiazine and penicillin have been used in our hospital for treatment of the complicating pneumonia, with the same good results as those obtained in the treatment of the usual bacterial pneumonia. As yet we have not used streptomycin in the treatment of whooping cough.

5. Some of our infants are dehydrated on admission, and some are also in a state of collapse. To these patients appropriate fluids are given by continuous intravenous injection.

6. Before each feeding, mucus is aspirated from the baby's throat. Our nurses feed the baby with a small nipple after the baby is temporarily taken out of the oxygen box. During the feeding, an oxygen tube and funnel is placed over the nurse's shoulder in case the baby becomes "blue" during the feeding.

7. Since whooping cough, proved bacteriologically, may be as mild as a five day cough or as severe as a cough persisting for nine months with paroxysms and

vomiting, it is indeed difficult to be entirely convinced of the efficacy of any new form of therapy. We have treated fewer patients than Dr. Kohn and Dr. Fischer, but we are of much the same opinion. We believe, on the basis of a small series of control and treated infants, that antipertussis serum (human) (a highly purified and concentrated globulin prepared from human donors immunized with H. pertussis, phase 1 ["hypertussis," Cutter Laboratories, Berkeley, Calif.]) definitely decreases the number and frequency of paroxysms in most infants. In very young infants, who were admitted with severe spells of choking and paroxysms, a definite improvement in their condition was noted when they were given 1 vial (2.5 cc.) intramuscularly daily for five days. This serum appeared to change the usually expected course of the disease in four to five days. The babies were in much less danger of choking with paroxysms, as the attacks were less frequent and less severe. Our preliminary results suggest that human pertussis immune serum is by far the most rational therapeutic agent yet used in the treatment of whooping cough. We feel, however, that more observations on control and treated patients should be made before any final judgment as to its value is made.

Of course, we are in agreement with Dr. Kohn and Dr. Fischer that with the careful detail they have outlined in the management of whooping cough many lives are saved that would otherwise be lost.

I emphatically endorse the belief, based on fairly good evidence, that whooping cough is a disease which can be prevented by prophylactic vaccination. I do not know of any instance in Canada in which phase I pertussis vaccine (killed with solution of formaldehyde or phenol) has been in the remotest way the cause of permanent disability or death in any child. I wish to reaffirm my belief that in the years to come, with a concerted effort made by physicians in vaccination and revaccination against whooping cough, this disease will become practically extinct, as has diphtheria with mass immunization with diphtheria toxoid in areas in which immunization programs have been reasonably complete.

Dr. Alfred E. Fischer, New York: It is gratifying that Dr. Aleman and Dr. Silverthorne are in essential agreement with the treatment which we have outlined. However, we have avoided the use of ether in oil by rectal or intramuscular administration because some years ago proctitis and sloughing followed its use in several patients. Dr. Silverthorne's point about the concentration of oxygen is well taken, and our experience is similar to his. We hope that the smaller hoods now in use will permit better regulation of oxygen.

We have used a refined rabbit serum in only 9 patients under 2 years of age. A satisfactory response was obtained in 2 patients, 6 were somewhat helped and 1 apparently not at all. Results with the human serum seemed to be much better. We concur in the statement that control cases are needed in order to be certain that any serum is effective in whooping cough. Yet it is extremely difficult to carry out controls in a disease as variable as whooping cough. Honest and critical clinical observation, after all, does have its place in estimating the response to any therapeutic procedure in a disease as well known as whooping cough.

Case Reports

ACETYLSALICYLIC ACID POISONING WITH RECOVERY

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URBANA, ILL.

ACETYLSALICYLIC acid and the other salicylates are among the least toxic of the commonly used active pharmacopeial preparations. Clinical reports of salicylate intoxication are relatively infrequent, though the quantities of these medicaments consumed throughout the world in the past fifty years have been enormous. The apparently benign status of these preparations, however, should not obscure the fact that certain grave hazards may be incurred when their use is abused.[1]

Most of the deaths reported have been caused by ingestion of methyl salicylate (oil of sweet birch, oil of wintergreen, oil of gaultheria, oil of betula) either accidentally or with suicidal intent. Methyl salicylate both in natural and in synthetic form is more toxic than other salicyl compounds in equivalent doses. In an analysis of 43 previously reported cases of methyl salicylate poisoning, in 41 per cent of which the patients were infants, the mortality rate was 59 per cent.[2] All the infants had drunk the oil of wintergreen from bottles left within their reach, and it was noted in this review that doses as small as 4 cc. had been lethal. Other salicylates may be toxic also, and an increasing number of cases of poisoning following therapeutic administration emphasizes the necessity for early recognition of the clinical symptoms and a knowledge of the proper corrective therapy. Death from salicylism has been reported in a 7 year old child whose psoriasis was treated externally with an ointment containing 5 per cent salicylic acid.[3] Fatal intoxication is not infrequent in cases of "acute salicylism" and has occurred in about 50 per cent of cases in which symptoms were serious enough to lead to hospitalization. All the salicylates except phenyl salicylate cause the same type of intoxication.[4]

Idiosyncrasy to salicylates manifests itself usually in the form of cutaneous rashes and anaphylactic phenomena. These reactions are due to unexplained hypersensitivity and may occur after the first administration of a small dose of salicylate. Acetylsalicylic acid is the compound

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From the Department of Pediatrics, Carle Hospital Clinic, Urbana, Ill.

1. Is Aspirin a Dangerous Drug? editorial, J. A. M. A. **124**:777 (March 18) 1944.

2. Stevenson, C. S.: Oil of Wintergreen (Methyl Salicylate) Poisoning, Am. J. M. Sc. **193**:772 (June) 1937.

3. Sannicandro, G.: Death from Application of Salicylic Acid Ointment, Dermosifilografo **12**:273 (July) 1937; in Fantus, B.: Yearbook of General Therapeutics, Chicago, The Year Book Publishers, Inc., 1937.

4. Goodman, L., and Gilman, A.: The Pharmacological Basis of Therapeutics, New York, The Macmillan Company, 1940.

oftenest involved, and the manifestations are usually urticarial, angioneurotic, asthmatic or erythematous in nature. Most of the allergic reactions to acetylsalicylic acid occur in patients with asthma and nasal polyps.[5] The symptoms due to idiosyncrasy are not to be confused with those of intoxication or poisoning.

We report 2 cases of acetylsalicylic acid poisoning in small children. These cases are of special interest in that both children had eaten large quantities of acetylsalicylic acid and had apparently relished it like candy. Acetylsalicylic acid has rarely been an offender in the reports of salicylate poisoning in the pediatric literature; moreover, children previously reported had usually received the preparations therapeutically over a considerable period.[6] Both our patients, seen on the same day, had consumed the acetylsalicylic acid in a period of an hour or less.

REPORT OF CASES

CASE 1.—C. M. W., a white boy aged 34 months, was first seen at 8 a. m. on Oct. 3, 1946. The medical history was irrelevant.

On October 2, at 11 a. m., he had been found seated on the floor in his foster home eating 5 grain (0.32 Gm.) acetylsalicylic acid tablets from a large bottle which had originally contained one hundred and seventy tablets. It was estimated by the supervisor of the home that he had ingested between fifteen and twenty of the 5 grain tablets within a period of one hour. When discovered, his mouth contained several partially disintegrated tablets. He was promptly given mustard water and he vomited food and some liquid. At 1:30 p. m. of the same day malaise was noted but there were no other symptoms. His temperature at that time was 37.2 C. (99 F.) (rectal) and the pulse rate 108 beats per minute. In the late evening restlessness and hyperpnea developed and persisted all night; at 8 a. m. on October 3 he was brought to the hospital.

Examination showed a well developed and well nourished boy; he was markedly hyperpneic, restless and irritable, and his face was flushed and anxious. His weight was 14.6 Kg. and his height 79 cm. The rectal temperature was 37.7 C. (99.9 F.). A specimen of urine was not obtained until 12 a. m.; urinalysis showed a 3 plus reaction for acetone and a positive reaction for diacetic acid. The carbon dioxide-combining power of the blood was 28 volumes per cent, and a complete blood count showed the hemoglobin content to be 10.4 Gm. per hundred cubic centimeters; the erythrocytes, 4,030,000, and the leukocytes, 18,600, with 73 per cent neutrophils, 26.5 per cent lymphocytes and 0.5 per cent monocytes. He was given 250 cc. of lactated Ringer's solution U. S. P. subcutaneously and sodium bicarbonate and fluids orally. He was nauseated but did not vomit. The hyperpnea restlessness and irritability increased after admission. By late afternoon he was delirious, and the hyperpnea was extreme. His condition appeared critical. The abdomen had become distended, and frequent loose, green stools were passed. He was given 300 cc. of a 1.5 per cent solution of sodium bicarbonate in distilled water intravenously at 5 p. m.; almost immediately there was lessening of the

5. Buchstein, H. F., and Prickman, L. E.: Allergic Reactions from Acetylsalicylic Acid (Aspirin), Proc. Staff Meet., Mayo Clin. **12**:616 (Sept. 29) 1937. Prickman, L. E., and Buchstein, H. F.: Hypersensitivity to Acetylsalicylic Acid (Aspirin), J. A. M. A. **108**:445 (Feb. 6) 1937.

6. Barnett, H. L.; Powers, J. R.; Benward, J. H., and Hartmann, A. F.: Salicylate Intoxication in Infants and Children, J. Pediat. **21**:214 (Aug.) 1942.

hyperpnea and restlessness, though he appeared semistuporous. Turpentine stupes were applied to the abdomen, with relief of the distention. The total liquid intake in the twenty-four hours after his admission was 1,630 cc. On the morning of October 4 the patient was moderately hyperpneic but drowsy and the rectal temperature was 37.8 C. (100 F.). He was completely rational and less irritable but listless. At 8:30 a. m. on October 4 the carbon dioxide–combining power was 44 volumes per cent, and the urine gave a negative reaction for acetone and diacetic acid. The blood count showed 9 Gm. of hemoglobin per hundred cubic centimeters, 3,430,000 erythrocytes and 8,950 leukocytes, with 61 per cent neutrophils, 37 per cent lymphocytes and 2 per cent monocytes. The rectal temperature on that day varied from 37.5 to 37.8 C. (99.5 to 100 F.). By evening the child was breathing normally.

He was discharged from the hospital on October 5, at which time physical examination showed an essentially normal condition: Urinalysis and a complete blood count made on the day of discharge gave essentially normal results. The carbon dioxide–combining power was 48 volumes per cent. Administration of sodium bicarbonate was continued orally for several days at home. The patient was seen again on October 10, at which time his examination showed a normal condition and he appeared well. At this last examination the urine was normal, the carbon dioxide–combining power was 48 volumes per cent and the prothrombin time 115 per cent of normal (Smith's bedside method). A complete blood count showed 10.7 Gm. of hemoglobin per hundred cubic centimeters, 3,780,000 erythrocytes and 8,800 leukocytes, with 52 per cent neutrophils, 43 per cent lymphocytes and 5 per cent eosinophils.

CASE 2.—L. A., a 3 year old white boy, was first seen at 8 a. m. on Oct. 3, 1946. The past medical history was irrelevant.

This patient, with another small child (case 1), had been found at 11 a. m. on October 2, eating 5 grain acetylsalicylic acid tablets, and it was estimated he had eaten fifteen or less within one hour. He was given an emetic and vomited; he seemed well all that day and played until bedtime. Early in the morning of October 3 he vomited and became hyperpneic.

This child did not appear seriously ill. He was moderately hyperpneic, and the rectal temperature was 37.5 C. (99.5 F.). His height was 79.6 cm. and his weight was 11.2 Kg. Physical examination showed an essentially normal condition except for hypertrophic tonsils. Urinalysis showed a specific gravity of 1.038, an acid reaction, a negative reaction for albumin, a faint trace of sugar, a 4 plus reaction for acetone and a positive reaction for diacetic acid. The blood count showed the hemoglobin to be 12.2 Gm. per hundred cubic centimeters; the erythrocytes, 4,530,000, and the leukocytes, 17,700, with 80.5 per cent neutrophils, and 19.5 per cent lymphocytes. The carbon dioxide–combining power of the blood was 14 volumes per cent. He was given 250 cc. of lactated Ringer's solution subcutaneously and later 400 cc. of a 5 per cent solution of dextrose in distilled water; sodium bicarbonate was given by mouth. By evening his respirations were normal. On the morning of October 4 the child appeared well; however, the carbon dioxide-combining power was only 27 volumes per cent, and the urine gave a 4 plus reaction for acetone and a positive reaction for diacetic acid. Three hundred and fifty cubic centimeters of a 1.5 per cent solution of sodium bicarbonate in distilled water was given intravenously. On October 5, urinalysis, including tests for acetone and diacetic acid, showed a normal reaction; the carbon dioxide–combining power was 38 volumes per cent, and the blood count showed 11.5 Gm. hemoglobin per hundred cubic centimeters, 4,300,000 erythrocytes and 7,050 leukocytes, with

38.5 per cent neutrophils, 41.5 per cent lymphocytes, 2.5 per cent monocytes, 15 per cent eosinophils and 2.5 per cent basophils. The child appeared entirely well, and he was discharged from the hospital. Sodium bicarbonate was administered orally at home for several days.

He was last seen on Oct. 10, 1946. At that time he appeared in good health; the urine was normal; the carbon dioxide–combining power was 46 volumes per cent; the prothrombin time, 100 per cent normal (Smith's bedside method), and the blood count showed 12.2 Gm. hemoglobin per hundred cubic centimeters, 4,170,000 erythrocytes and 12,050 leukocytes, with 49.5 per cent neutrophils, 41.5 per cent lymphocytes, 8.5 per cent eosinophils and 0.5 per cent basophils.

COMMENT

The most prominent symptom in the clinical picture was hyperventilation. Despite the fact that the degree of acidosis, as indicated by the carbon dioxide–combining power of the blood, was greater in case 2, the patient was less hyperpneic and never appeared as seriously ill as the first child. Cyanosis was not noted in either child, and vomiting, fever and dehydration were not pronounced. The irritability and delirium noted in case 1 were striking, and during the period the latter persisted the patient appeared about to die. Eosinophilia was noted in two successive blood counts in case 2. Of interest was the latent period (twelve to twenty-four hours) between ingestion of the acetylsalicylic acid and the appearance of definite intoxication.

Though the toxicity of salicylates has been definitely established, a difference of opinion exists as to the exact mechanism by which injury is produced. The theories of various authors, enumerated in the report of Troll and Menten in 1945,[7] postulate the following etiologic factors: (1) an acidosis leading to hyperpnea; (2) direct stimulation of the respiratory center, leading to hyperpnea and ending in acidosis; (3) an increase in the basal metabolic rate, and (4) a prolongation of the prothrombin time. Hartmann[8] favored the theory that the primary hyperventilation is a result of central stimulation, with subsequent alkalosis resulting from a deficit in carbon dioxide, an alkaline urine and compensatory reduction in the bicarbonate of the blood. Then ketosis develops and produces a real bicarbonate deficit acidosis; ketosis can be abolished only with repeated injections of sodium r-lactate or sodium bicarbonate. In the 2 cases we report it was not possible to determine whether the acidosis or the hyperpnea was primary, since both were present when the patients were first seen.

Link and associates[9] observed that a single dose of salicylic acid given to rats which had been fed a diet low in vitamin K produced a decrease in the prothrombin of the blood; also, if the salicylic acid was given over a considerable period hemorrhages occurred. Postmortem

7. Troll, M. M., and Menten, M. L.: Salicylate Poisoning, Am. J. Dis. Child. **69**:37 (Jan.) 1945.

8. Hartmann, A. F.: Acute Salicylate Poisoning, J. Pediat. **26**:214 (March) 1945.

9. Link, K. P.; Overman, R. S.; Sullivan, W. R.; Huebner, C. F., and Schell, L. D.: Studies on the Hemorrhagic Sweet Clover Disease, J. Biol. Chem. **147**:463 (Feb.) 1943.

studies on patients with acetylsalicylic acid poisoning have shown the main pathologic change to be widespread hemorrhage from capillaries in the serous surfaces and supportive structures. Hemorrhages have been observed consistently in the pleurae, pericardium, omentum, meninges and the His and Virchow-Robin [7] spaces; Stevenson [2] stated that the changes in salicylate poisoning are primarily vascular.

When patients are seen shortly after the ingestion of a massive dose of a salicylate, gastric lavage is indicated. The 2 children reported here were not seen until twenty hours after the preparation had been ingested and hyperpnea had developed.

Dodd and her co-workers [10] emphasized the importance of administration of large amounts of fluids in the treatment of salicylate intoxication. Barnett and associates [6] advocated the use of alkali, recommending sodium r-lactate as the preparation of choice. They stressed in addition the administration of large amounts of dextrose, postulating that the susceptibility to salicylate intoxication depended on an inadequacy of glycogen reserve. Olmsted and Aldrich [11] administered sodium bicarbonate by mouth and rectum in the treatment of salicylate intoxication.

In our experience, limited to 2 cases only, the clinical improvement which followed intravenous administration of solution of sodium bicarbonate was prompt and gratifying. In the more seriously ill patient, the hyperpnea diminished almost immediately after the infusion of this solution. Decrease of the acidosis, as judged by the carbon dioxide–combining power of the blood and the disappearance of ketone bodies from the urine, was also noted shortly after the intravenous sodium bicarbonate therapy. Since lactated Ringer's solution was given neither intravenously nor in adequate quantities subcutaneously, an opinion as to the true merits of one solution over the other in salicylate intoxication cannot be expressed.

SUMMARY

Two cases of salicylate intoxication in small children due to the ingestion of massive single doses of acetylsalicylic acid are reported. Salicylate poisoning from acetylsalicylic acid is uncommon; moreover, the few reported cases of poisoning from this preparation usually occurred when the drug had been administered therapeutically. The possibility of accidental poisoning from this commonly used household remedy should be borne in mind when there are small children in the home. Both of our patients responded promptly and satisfactorily to the intravenous administration of solution of sodium bicarbonate.

Carle Hospital Clinic.

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10. Dodd, K.; Minot, A. S., and Arena, J. M.: Salicylate Poisoning: An Explanation of the More Serious Manifestations, Am. J. Dis. Child. **53**:1435 (June) 1937.

11. Olmsted, J. G. M., and Aldrich, C. A.: Acidosis in Methyl Salicylate Poisoning: Report of Two Cases and a Review of the Literature, J. A. M. A. **90**:1438 (May 5) 1928.

News and Comment

GENERAL NEWS

Hugh K. Berkley Memorial.—A fund-raising campaign has been started for the Hugh K. Berkley Memorial Fund. It is planned to use this money to build and equip a new medical amphitheater at the Children's Hospital of Los Angeles, which will be named for Dr. Berkley. Contributions should be sent to "Children's Hospital Society, Hugh K. Berkley Memorial Fund," % Children's Hospital, 4614 Sunset Boulevard, Los Angeles 27.

Journal of Child Psychiatry.—A new journal, the *Journal of Child Psychiatry,* is being published by the Child Care Publications of New York city. This journal enters a field which is greatly in need of exploitation.

Appointment of Dr. Reilly as Head of Department of Pediatrics, University of Arkansas.—The University of Arkansas School of Medicine announces the addition to its staff of Dr. William A. Reilly as professor and head of the department of pediatrics. Dr. Reilly was recently associated with the department of pediatrics of the University of California. His appointment in Little Rock is one of a series recently made in line with the university's policy of establishing full time headships in all its clinical departments. The department of pediatrics will be heavily supported by a grant from the Children's Bureau, secured through the offices of the Arkansas State Department of Health.

Abstracts from Current Literature

Metabolism; Infant Feeding; Milk and Other Foods

THE EFFECT OF THE CITRATE ION ON THE CALCIUM METABOLISM OF ADULT HUMAN SUBJECTS. F. R. STEGGERDA and H. H. MITCHELL, J. Nutrition **31**:423 (April) 1946.

The authors found that calcium citrate was approximately as well utilized by the adult human as was calcium gluconate. Citrates did not appreciably modify the utilization of the calcium in a basal low calcium diet.

FREDEEN, Kansas City, Mo.

THERAPY OF TOXICOSIS IN THE INFANT. GIULIO MURANO, Pediatria **54**:1, 1946.

On the basis of reports made at the Sixteenth Italian Pediatric Congress, the author emphasizes that the treatment for toxicosis in the infant has been augmented by three therapeutic means: the plasma transfusion, the hypertonic solution of sodium chloride and the sulfonamide drugs.

On the basis of personal observation, he discusses the probable mechanism of action of these important therapeutic aids, especially their application and indications.

From these considerations, and from the most recent observations on metabolic disturbances and on the clinical picture (more than ever protean) of functional secondary adrenal insufficiency, the author is inclined to the opinion that in the pathogenesis of this complicated syndrome peculiar to infancy one should consider also the possibility of a functional deficiency of the adrenal cortex.

FROM THE AUTHOR'S ABSTRACT.

Vitamins; Avitaminoses

RICKETS RESISTANT TO VITAMIN D: HEALING WITH VERY HEAVY DOSAGE OF VITAMIN D, FLUCTUATIONS IN VITAMIN D REQUIREMENT, DEVELOPMENT OF TOXIC SYMPTOMS, AND OF NON-RACHITIC CHANGES IN BONES. HELEN MACKAY, and Q. I. MAY, Proc. Roy. Soc. Med. **38**:563 (August) 1945.

A case of rickets in a girl aged 7 years is reported. The report is accompanied with roentgenograms of the long bones.

WILLIAMSON, New Orleans.

RICKETS RESISTANT TO VITAMIN D: HEALING WITH VERY HEAVY DOSAGE OF VITAMIN D, FLUCTUATIONS IN VITAMIN D REQUIREMENT, DEVELOPMENT OF HYPERCALCAEMIA. HELEN MACKAY and Q. I. MAY, Proc. Roy. Soc. Med. **38**:565 (August) 1945.

A case of rickets in a girl aged 16 years is reported.

WILLIAMSON, New Orleans.

BERIBERI IN INFANTS. EUGENE STRANSKY, Ann. paediat. **166**:269 (May) 1946.

Beriberi in the infant is not a pure simple deficiency disease. Two factors are involved: (1) thiamine deficiency, and (2) intake of toxic intermediary products

of carbohydrate metabolism in the milk of the nursing mother, whose metabolism is disturbed by insufficient vitamin supply. Signs and symptoms of infantile beriberi are discussed, with emphasis on "breast milk intoxication."

FROM THE AUTHOR'S ABSTRACT.

Hygiene; Growth and Nutrition; Public Health

THE PRESENT DAY PROBLEMS OF PROTECTION OF CHILDREN'S HEALTH IN WARTIME. M. D. KOVRIGINA, Pediatriya **3**:11, 1943.

The author points out the important place that child welfare work occupies on the program of the Health Department of the United Soviet Socialist Republics. This great interest in child welfare shown by the government of the United Soviet Socialist Republics was especially well demonstrated in wartime when, rather than being curtailed, the activities of the Public Health Department were intensified, and the child welfare program was greatly expanded.

The evacuation of large masses of children during wartime, as well as the increase in the number of working mothers in both urban and rural communities, created numerous problems requiring the immediate institution of wide networks of nurseries and medical facilities for the care of children. The most important child health problems created by war conditions became the control of communicable diseases and the fight against rickets and other deficiency diseases, especially among the large masses of evacuated children.

Special wartime legislative measures were passed in the attempt to meet these needs in spite of wartime shortages. Additional facilities for the care of evacuated children and children of working mothers were established under the direct medical supervision of the Public Health Department. An energetic fight against major epidemics has been successfully conducted by the Public Health Department. Health education in schools was intensified. Even provisions for the increase of salaries of public health physicians were made in recognition of the increased burden carried by them in wartime.

The author reports that infant mortality in the first year of life showed a slight rise in 1941 and 1942 as compared to 1940. However, a definite drop in the infant mortality was noted during the second half of 1942. As in prewar times the main causes of death constitute the acute gastrointestinal disorders and pneumonia.

The control of deficiency diseases among children in presence of wartime shortages has been one of the most difficult tasks confronting the Public Health Department, and one requiring great ingenuity. Special milk rationing for children was instituted. However, in spite of the special preference shown to children it was possible to allot only 7 liters of cow's milk per month for infants up to 1 year of age, and 5 liters per month for infants from 1 to 3 years of age. Special emphasis was placed on the organization of rural nurseries and ambulatory child hygiene clinics in order to free the greatest number of mothers for work in the fields, and thus increase the country's food production.

It is also reported by the author that the wartime public health problems have been incomparably greater in the liberated areas where practically all of the institutions for the care of children have been destroyed by the enemy, and where epidemics have been raging among the starving population.

BODER, Los Angeles.

Prematurity and Congenital Deformities

CONGENITAL DEFORMITIES: TWO CASES. G. O. TIPPETT, Proc. Roy. Soc. Med. **38**:568 (Aug.) 1945.

Case 1 was that of a male child who was born with defective arms. On the left side the structure stopped short in the forearm, the stump having a thumb and a rudimentary digit; on the other side there was complete absence of an upper limb. Although the clavicle on this side was developed, only a small osseous fragment represented the scapula.

Case 2 was that of a female child with defective lower limbs. Both the hips and the knees were acutely flexed, while the ankles were in talipes calcaneovalgus. The joint and muscles of the limb were normal.

WILLIAMSON, New Orleans.

Newborn

COMPLETE AURICULOVENTRICULAR BLOCK IN A FETUS: CASE REPORT. R. K. PLANT and R. A. STEVEN, Am. Heart J. **30**:615 (Dec.) 1945.

The authors report a case in which the fetal heart rate one month prior to delivery varied between 50 and 60 per minute. The rate was regular and not affected by pressure on the fundus. Examination a few hours after birth revealed a baby normally pink in color and with normal respiration. The heart rate was 52 per minute. The electrocardiogram showed complete auriculoventricular dissociation with an auricular rate of 114 and a ventricular rate of 50. Roentgenograms showed pronounced cardiac enlargement. After a few days the baby began to fail and became cyanotic. Death occurred on the sixth day.

Examination at autopsy failed to reveal any gross structural defects in the heart. The heart was, however, enlarged, weighing 56 Gm. (normal 20.6 Gm.). Microscopic study of the heart failed to show any fibers which could be identified as belonging to the bundle of His. It was believed that the heart block resulted from absence or faulty development of the bundle.

GIBSON, Chicago.

CONGENITAL DEFECT OF THE ABDOMINAL WALL IN THE NEW BORN. FRANK S. JOHNS, Ann. Surg. **123**:886 (May) 1946.

The congenital defect gastroschisis is rare. The author found reports of 96 cases. Sixty-eight of these cases were of stillborn monsters; 19 were of children living at birth and normal except for the defect of the abdominal wall on whom no attempt at repair was made, and 9 were of children on whom an attempt at repair was made.

The author summarizes the 9 cases in which operation was performed and reports a case of his own.

BANTIN, Omaha.

CONCLUSIONS FROM A STUDY OF 7 MILLION BIRTHS. JACOB YERUSHALMY, California & West. Med. **63**:198 (Oct.) 1945.

From a study of the live births and stillbirths of more than 7,000,000 American babies in the five years from 1937 to 1941 comes important evidence in support of the child-spacing theory. This is the medical opinion now commonly held that a mother needs a period of rest and recuperation between the birth of one child and the beginning of another pregnancy.

Dr. Jacob Yerushalmy, principal statistician in the United States Public Health Service, has found that the length of time between pregnancies has an important relation to the possibility that the gestation will end in the tragedy of a stillbirth. More than 75,000 babies are lost each year through stillbirths.

Precisely how long the average space between births should be to reduce the danger of stillbirth to a minimum, Dr. Yerushalmy was unable to indicate from his study. He did conclude, however, that "relatively short intervals (between pregnancies) and relatively long intervals are associated with higher stillbirth rates while moderate intervals lead to the lowest rates."

The results of his study appeared in detail in the May 1945 issue of *Human Biology*, page 65.

PRYOR, Redwood City, Calif.

ATELECTASIS OF THE NEWBORN. HAROLD OWENS, California & West. Med. **63**:225 (Nov.) 1945.

In 23 cases of atelectasis of the newborn bronchoscopic examinations were made during the eighteen months prior to this report, with gratifying results.

Wilson and Farber feel that in many instances lack of expansion of the lungs in premature infants is not a failure of the respiratory effort, although this may be weak, but that the atelectasis is due to cohesion of moist surfaces of the air passages.

The author summarizes his conclusions as follows:

1. The etiology of atelectasis in the newborn is not fully understood.

2. In selected cases atelectasis of the newborn secondary to bronchial obstruction which fails to respond to conservative treatment is materially benefited by bronchoscopic aspiration.

3. Most cases of atelectasis occur in premature infants.

4. Bronchoscopic aspiration in the newborn infant is a relatively benign procedure when properly performed.

5. The improved 3 mm. Jesberg bronchoscope is the instrument of choice in cases of atelectasis in the newborn.

PRYOR, Redwood City, Calif.

CHOICE OF SULPHONAMIDE IN THE TREATMENT OF OPHTHALMIA NEONATORUM. ARNOLD SORSBY and E. E. HOFFA, Brit. J. Ophth. **29**:141 (March) 1945.

On the basis of 333 cases of ophthalmia neonatorum treated with a standard dose of five sulfonamide compounds, it is concluded that the least tolerated drug is sulfanilamide and that sulfapyridine is less well tolerated than sulfamezathine, sulfathiazole or sulfadiazine.

In their efficacy against the infection, as distinct from their toleration by the babies, these five substances are not strikingly different.

With the standard dose employed in this series, some 30 to 40 per cent of infants show clinical cure within three days. Well over 80 per cent of the total are cured by the end of eight days' treatment.

Gonococcic ophthalmia neonatorum responds more readily than other varieties of ophthalmia. In cases showing inclusion bodies the response is satisfactory. All initial severity does not affect the course unfavorably. In many severe cases the condition clears rapidly. Irrespective of the causal organism, the response is sluggish or poor in some 15 per cent of cases. The routine management of cases is described.

W. ZENTMAYER [ARCH. OPHTH.].

PHYSIOLOGIC DECREASE IN WEIGHT IN THE NEWBORN. PASQUALE BUONOCORE, Pediatria **54**:42, 1946.

From the ocurrence of hyperglycemia and ketonemia in the newborn infant, the author concludes that during the period of physiologic loss of weight energy changes take place along with heightened metabolism of fat substances, both food fat and body fat. This increased metabolism of fats constitutes the metabolism of transition between the fetal state and the metabolically autonomous extrauterine life, and therefore it may act to limit the neonatal period and to give it a particular biochemical character.

FROM THE AUTHOR'S ABSTRACT.

Acute Contagious Diseases

TREATMENT OF PREPARALYTIC POLIOMYELITIS WITH GAMMA GLOBULIN. ANNE M. BAHLKE and JAMES E. PERKINS, J. A. M. A. **129**:1146 (Dec. 22) 1945.

A study of the possible therapeutic effect of the gamma globulin fraction of pooled plasma on preparalytic poliomyelitis was made in Elmira, N. Y., and Boston in August and September 1944. The authors came to the following conclusion:

"In summary it can be conclusively stated that, in a series of 111 patients with preparalytic poliomyelitis observed for approximately six months after onset, no benefit is detectable when 56 of them who had received large doses of gamma globulin intramuscularly in the preparalytic stage are compared with 55 alternate, untreated controls.

"As a corollary to the foregoing conclusion, these data compiled with gamma globulin offer further indication that serum in any form is, for all practical purposes, ineffective in the therapy of poliomyelitis."

BAIRD, Wauwatosa, Wis.

A STUDY OF THE ORIGIN OF AN EPIDEMIC OF POLIOMYELITIS. MARTHA L. SMITH, EDWARD M. BRIDGE, HELEN E. UNDERWOOD and GRACE E. DALE, J. A. M. A. **129**:1150 (Dec. 22) 1945.

Investigation of illnesses occurring in contacts of the first 3 paralytic patients in the 1944 epidemic of poliomyelitis in Buffalo indicates that the disease had probably been occurring as an unrecognized minor illness for three months previously. This reduces to two months the interval between the first case of 1944 and the last one of the previous year.

The incidence in the community of illness highly suggestive of nonparalytic poliomyelitis was at least five times that of the recognized disease. The evidence suggests that the disease was spread by direct human contacts.

BAIRD, Wauwatosa, Wis.

POLYCYTHEMIA IN THE COURSE OF MALIGNANT DIPHTHERIA. P. SEDALLIAN and P. MONNET, Presse méd. **53**:381 (July 14) 1945.

The presence of polycythemia during the course of malignant diphtheria is evidence of adrenal cortex deficiency, and the return of the blood count to normal indicates the correction of this deficiency. The authors present case histories which show how the utilization of this simple criterion will indicate the proper method of treatment.

DAFFINEE, Melrose, Mass.

CYTODIAGNOSIS OF MUMPS FROM PAROTID SALIVA. R. SOHIER and M. LEVRAT, Presse méd. **53**:393 (July 21) 1945.

Hundreds of samples of saliva obtained directly from Stensen's duct were studied cytologically. Early cases of mumps presented a uniform picture, which the authors conclude is diagnostic for that disease. DAFFINEE, Melrose, Mass.

TRANSMISSION OF POLIOMYELITIS TO THE WHITE MOUSE. J. VIEUCHANGE, Presse méd. **53**:435 (Aug. 11) 1945.

The Lansing strain of poliomyelitis virus, isolated by Armstrong, was sent to France. Experimental results have confirmed Armstrong's conclusions. Histopathologic studies show the typical changes of poliomyelitis. Despite repeated transmission through mice, the virus retains its virulence—indeed after a series of passages it may become more virulent. The virus was found to be pathogenic for monkeys even after forty-four passages through mice.

Vieuchange points out that the different strains of poliomyelitis virus may be as individual, immunologically speaking, as the different strains of encephalitis.

DAFFINEE, Melrose, Mass.

RELATION OF SALIVARY AND PANCREATIC AMYLASE TO EPIDEMIC PAROTITIS IN INFANCY. ALESSANDRO ZANINI, Pediatria **54**:60, 1946.

In 10 cases of children with epidemic parotitis, the author has studied the salivary and pancreatic amylolytic power and comes to the following conclusions:

1. Salivary amylolysis decreases remarkably at the end of the first week of illness and becomes normal about the fifteenth day.

2. The pancreatic amylolytic power increases notably at the end of the first week of illness and becomes normal about the fifteenth day.

3. In these cases there was no endocrine relation between the salivary glands and the pancreas, but the pancreatic substitutive response to the decreased function of salivary glands is nothing more than a response of the exocrine pancreas to an augmented demand for amylolytic enzymes. FROM THE AUTHOR'S ABSTRACT.

PHENOMENON OF THE DISAPPEARANCE OF THE MEASLES ERUPTION ON ADMINISTRATION OF MEASLES CONVALESCENT SERUM. S. BERSATTI, Pediatria **54**:102, 1946.

In a series of experiments with measles convalescent serum the author demonstrated how the intradermal injection of from 0.3 to 0.5 cc. of the serum into maculopapules did not cause even the maculopapules to disappear and how the intradermal injection of 0.5 cc. of the serum at the time of the initial exanthem on the neck and face did not aid in avoiding the appearance of maculopapules in the zone of injection. Only with doses of from 3 to 5 cc. did he notice the exanthem of the zone of injection growing pale as compared with the exanthem of the adjacent zone. FROM THE AUTHOR'S ABSTRACT.

MIXED INFECTION IN VARICELLA WITH FOCAL NECROSES, GRANULOMAS AND HEMORRHAGES IN INTERNAL ORGANS. A. STUDER, Ann. Paediat. **166**:238 (May) 1946.

In a premature baby who had died at the age of 5 weeks of purulent varicella, hemorrhages, areas of necrosis and granulomas were observed in the liver, spleen,

kidneys, adrenal glands and heart. On the basis of the morphologic aspect of these changes, a diagnosis of septicemia would be refuted in spite of the presence of pathogenic bacteria. A change in behavior of the organism due to the presence of the varicella is responsible for its ability to respond to a bacterial infection with the formation of granulomas.

The staining method introduced by Turewitsch for Paschen bodies is, with a modification, recommended for the staining of Kupffer cells in the liver and skeletal muscles.

FROM THE AUTHOR'S ABSTRACT.

Acute Infectious Diseases

RHEUMATIC FEVER CASE-FINDING PROGRAM IN TWO CALIFORNIA COUNTIES. HELEN M. JOHNSON, California & West. Med. **63**:123 (Sept.) 1945.

It is unfortunate that there is still no specific test for rheumatic fever such as the tuberculin, the Wassermann or the agglutination test. In the absence of a specific test, it is necessary to make a complete work-up of each case to rule out other diseases. Often it is necessary to make serial examinations for months before a diagnosis can be made. This procedure is time consuming, and the limited personnel in this rheumatic fever program does not permit a mass survey technic, such as can be used in tuberculosis case finding.

The sedimentation rate is one of the most useful aids in following the patient with rheumatic fever to determine when the active phase passes into the inactive phase. However, it is a nonspecific test, and the rate is increased in cases of tuberculosis and osteomyelitis, two diseases from which rheumatic fever must be differentiated. The rate may be normal in cases of pure chorea and in cases of decompensation—increasing only when the decompensation has disappeared. It is frequently normal in patients referred to the clinic with a history of recent vague aches and pains, epistaxis and excessive fatigue, and of course occasionally in a patient whose condition has been diagnosed elsewhere as active rheumatic fever. One wonders whether one is treating subacute rheumatic fever or merely chronic fatigue—but in either instance with treatment the child puts on weight, regains his appetite and the fatigue disappears. Of course, the diagnostic label of "rheumatic fever" is not given to such a child unless there is undoubted evidence of the disease.

It is often difficult for the family, and sometimes even for the family doctor, to realize the necessity of prolonged convalescence for a child with a monocyclic type of rheumatic fever associated with a rapid return of a feeling of well-being, which is present as long as the child remains in bed. When the child is released from his bed too soon, the rapidly returning symptoms of fatigue, irritability, nervousness and poor appetite stress the importance of a longer convalescence.

PRYOR, Redwood City, Calif.

PREVENTIVE AND PUBLIC HEALTH ASPECTS OF RHEUMATIC FEVER IN CHILDREN. EDITORIAL. J. C. GEIGER, California & West. Med. **63**:159 (Oct.) 1945.

Rheumatic fever is today one of the foremost health problems of childhood. Between the ages of 5 and 9 years, deaths from this disease are outnumbered only by deaths from the four principal communicable diseases of childhood. Between the ages of 10 and 14 it is the leading cause of death, and between the ages of 15 and 24 it is second only to tuberculosis.

The economic importance of rheumatic fever is much greater than that of poliomyelitis, but the relative attention given the two diseases by the lay public, the

health authorities and the vital statisticians presents a striking contrast. The statistics on deaths from heart disease give only an inkling of the relative part played by rheumatic fever.

The magnitude of the problem of rheumatic heart disease is recognized by health officials. The statistical estimates of the death rate from heart disease in the age group from 5 to 24 years are an indication of the prevalence of rheumatic heart disease. Sanatorium care for rheumatic heart disease is the most logical means both of lessening the severity of the infection and of checking possible recurrences. It is also believed worth while to try the effect of change from a cold, damp region to a warmer one.

Specific home care for persons discharged from sanatoriums is likewise deserving of special consideration. It is hoped that the medical and the lay population will come to recognize that sanatorium care is as important for rheumatic heart disease as it is for active tuberculosis.

PRYOR, Redwood City, Calif.

PENICILLIN IN TETANUS. W. A. ALTEMEIER, J. A. M. A. **130**:67 (Jan. 12) 1946.

Sixteen patients with tetanus are reported on, 11 of whom were children 10 years of age or less. All received tetanus antitoxin U. S. P. in doses of from 20,000 to 390,000 units. In 9 patients the wounds were excised. Thirteen were given penicillin, usually in doses of 15,000 units every three hours.

Ten patients died and 6 recovered: nine of the patients treated with penicillin died, 8 of respiratory arrest. The deaths were directly related to the shortness of the incubation period of the disease. The penicillin therapy failed to show any beneficial effect except in 1 patient, who had a superimposed pneumonia.

BAIRD, Wauwatosa, Wis.

FREQUENCY OF INFANTILE APPENDICAL OXYURIASIS IN URUGUAY. JOSE LOPEZ FERNÁNDEZ, Arch. de pediat. d. Uruguay **17**:169 (March) 1946.

In 88 careful consecutive examinations of surgically removed appendixes, the author recovered the oxyuris in 32 appendixes, or 36.3 per cent. He remarks that in addition to young, nongravid males and females, he encountered fertilized females with uteri full of eggs in all the parasitized appendixes.

The author discusses the frequency and treatment of intestinal oxyuriasis and states that a review of the literature indicates that this condition is encountered in from 16.5 to 48.5 per cent of surgically removed appendixes. The number of parasites is generally small. In the author's series most of the parasitized appendixes were removed from girls.

PLATOU, New Orleans.

Chronic Infectious Diseases

THE TUBERCULIN INDEX IN PARISIAN CHILDREN. M. LELONG and A. C. MACLOUF, Presse méd. **53**:337 (June 23) 1945.

From 1942 to 1945, 12,530 children and young people between the ages of 4 and 20 years were left temporarily at the Depot of Child Care in Paris. The Pirquet test was made on all these children, and the results are summarized by the authors. The percentage of reactors increased from 11.76 per cent, in the 4 year old group, to 63.8 per cent, in the 18 year old group. This curve is less than that obtained in 1934 by Lereboullet and his associates, whose work showed positive reactors in 27.5 per cent of the 5 year old group and in 75 per cent in the 15 year old group. A similar study of school children by Bezançon and his associates in 1943 showed

positive reactors in 13.04 per cent of the 4 year old group and in 61.34 per cent of the 18 year old group.

The authors point out that, although the mortality rate and the morbidity rate have decreased tremendously, the number of reactors to the cutaneous tests has not decreased so strikingly. They also stress that an unfavorable environment will produce more reactors and that, for this reason, the figures for their series are not in agreement with the figures from the public schools, since the majority of their patients came from much less hygienic surroundings.

Their figures also show a larger number of reactors among the boys of any of the age groups than among the girls of the corresponding groups. They are unable to explain this fact, which is exactly opposed to the observations of Nobecourt and Briskas in 1936, in their study of hospital admissions from 1921 to 1935.

DAFFINEE, Melrose, Mass.

ANTITUBERCULOSIS VACCINATION BY INHALATION. J. TROISIER, J. BRETEY and J. SIFFERLEN, Presse méd. **53**:349 (June 30) 1945.

Guinea pigs were subjected to varying concentrations of a vaporized emulsion of vaccine (bile Calmette-Guérin vaccine) for several exposures. Two and three years afterward, when the reactions to the intradermal tuberculin tests had become negative, an injection of live tubercle bacilli was given. The guinea pigs which had received a heavy concentration of BCG vaccine showed no tuberculous lesions, while those receiving a lesser amount of the vaccine showed lesions throughout the body.

The authors conclude that the immunity produced by BCG vaccine can be established by inhalation as well as by injection. They also point out that immunity may persist even after the allergic response to tuberculin is lost.

DAFFINEE, Melrose, Mass.

Diseases of Blood, Heart and Blood Vessels and Spleen

RIGHT SIDED AORTIC ARCH: CASE REPORT. E. E. FONG, Am. J. Roentgenol. **55**:452 (April) 1946.

The author reports an asymptomatic case of this anomaly. He points out that this condition may cause dysphagia and symptoms of pressure under the sternum. These symptoms and a right-sided aortic "knob" have often led to an erroneous diagnosis and fruitless operation.

HARRISON, Chicago.

GRAVIMETRIC METHOD WITH COPPER SULFATE FOR DETERMINATION OF THE HEMOGLOBIN, HEMATOCRIT READING AND TOTAL PROTEINS OF THE BLOOD. MARIO SAGGESE and ARRIGO DE LUCA, Pediatria **54**:106, 1946.

The authors present the technic and the principles of the gravimetric method with the use of copper sulfate for determination of the hemoglobin, the hematocrit reading and the total proteins of the blood. In this report they give the results obtained from researches made in collaboration with the Italian Medical Nutrition Mission, and add to these the results of successful investigations on control of the determination of plasma proteins. From the first results the authors come to the conclusion that the method may be used for clinical research, especially by pediatricians.

FROM THE AUTHOR'S ABSTRACT.

INFECTIOUS LYMPHOCYTOSIS. ELBIO E. DE LOS SANTOS, Arch. de pediat. d. Uruguay **17**:158 (March) 1946.

After reporting a case of this interesting disease, the author reviews the typical course and features which differentiate it from similar hematologic disorders in young children. He assumes that benign infectious lymphocytosis is caused by a virus.

PLATOU, New Orleans.

Diseases of Nose, Throat and Ear

DEAFNESS—A MODERN APPROACH TO ITS TREATMENT. W. D. CURRIER, California & West. Med. **64**:126 (March) 1946.

It might be said that in no other field of medicine is more pessimism and defeatism to be encountered than in that of the treatment of deafness. The following statements were made by so-called authorities in the field of otology: "Nothing can be done for deafness." "The patient has nerve deafness; so there is no treatment." "Your child is congenitally deafened, and there is nothing that can be done. When he will be 5 or 6 years old, institutionalize him in a school for the deafened."

Fortunately, not one of these statements is true. But the disturbing fact remains that physicians in general, and otologists in particular, so easily accept defeat in the treatment of deafness. Not even in the care and treatment of patients with cancer has a comparable attitude of pessimism been allowed to become established, almost without a challenge. But whereas cancer is notably a disease of old age, usually occurring in persons who have passed the prime of their active life, deafness is most frequent, and therefore most harmful, in childhood and youth. Moreover, the number of persons handicapped by deafness is much larger than the number of patients suffering from cancer. It would, therefore, be no more than a socially and economically logical procedure to institute the most comprehensive research for the study and treatment of deafness. There is a great need for a few heavily endowed institutions with the sole purpose of furthering the research and advancing the clinical treatment of deafness.

It is most difficult to arrive at a diagnosis of deafness in an infant or in a child under 4 or 5 years of age. If the child is totally or severely deafened, the parents may note that it sleeps in spite of loud noises in its immediate vicinity, or that it fails to respond when spoken to. But generally deafness will be suspected only if the child does not learn to talk, or if he articulates with a pronounced speech defect. Since the child is unable to hear, he is equally incapable of reproducing sounds correctly. All too frequently such children are judged by lay persons to be, and even diagnosed by physicians as, mentally defective. Institutions for the feebleminded contain many children whose only defect is a hearing deficiency.

Thirty-two possible procedures which may be applied in the treatment of deafness are enumerated.

The choice of treatments and procedures from which the patient is likely to derive the greatest benefit will depend on the characteristics of the individual case. But the fact that such a large selection of methods has been evolved should dispel the notion that nothing can be done for deafness.

PRYOR, Redwood City, Calif.

PARENTERAL INFECTIONS IN GASTRO-ENTERITIS WITH SPECIAL REFERENCE TO MASTOIDITIS. M. E. WEHNER, Proc. Roy. Soc. Med. **38**:561 (Aug.) 1945.

The author presents a brief analysis of all cases of infants under 1 year who were admitted to the hospital with gastroenteritis in 1944, with particular reference

to any associated infection. A large proportion of the babies were under 6 months of age, the incidence of the occurrence of diarrhea diminishing as the infants approached 1 year of age. The degree of dehydration varied from minor to severe. Rectal swabs were taken in an attempt to determine whether an enteral infection was present. In only 1 case was a pathogenic organism isolated. Many of the parenteral infections were extremely severe, some of the children having a double infection as well as the diarrhea. All patients were given the same general treatment. Sulfonamide drugs were used when necessary. Mastoidectomy was performed on 15 of the patients, in 12 of whom pus was encountered.

The report is accompanied with two tables—one showing mortality and degree of dehydration according to age group, and the other showing relation of parenteral infection to mortality. The author discusses the fatal cases.

WILLIAMSON, New Orleans.

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

FURTHER OBSERVATIONS UPON IMPERFORATE ANUS. ROBERT L. RHODES, Ann. Surg. **123**:877 (May) 1946.

This malformation occurs in about 1 of every 5,000 babies born.

The author outlines his technic of operation, which he feels produces better results than the technic advocated in textbooks on surgery. He reports 4 cases.

BANTIN, Omaha.

CONGENITAL ATRESIA OF THE ESOPHAGUS WITH TRACHEO-ESOPHAGEAL FISTULA. HARRY A. KEENER and ROBERT C. HICKEY, California & West. Med. **64**:128 (March) 1946.

The authors report a not infrequent anomaly of the gastrointestinal tract, congenital atresia of the esophagus with tracheoesophageal fistula. They demonstrate the antemortem diagnostic roentgenographic findings and show, also roentgenographically, the pathoanatomic changes, as seen at necropsy.

Why these esophageal malformations occur is a matter of conjecture. An incorrect cleavage of the longitudinal infoldings has been used frequently as a descriptive aid in understanding congenital esophageal atresia with or without fistula. This fits well with Vogt's classification.

The authors also discuss the diagnosis and treatment of this anomaly and report 2 cases from a United States Naval Hospital. PRYOR, Redwood City, Calif.

THE RETENTION OF ELECTROLYTE DURING RECOVERY FROM SEVERE DEHYDRATION DUE TO DIARRHEA. DANIEL C. DARROW, J. Pediat. **28**:515 (May) 1946.

Balances of nitrogen, sodium, chloride, potassium, phosphorus and calcium during recovery of infants from dehydration due to severe diarrhea are reported. The balances are correlated with each other so as to make apparent the disturbances in composition of the intracellular as well as the extracellular fluids.

Diarrhea led to decrease in extracellular water, owing to loss of sodium and chloride in extracellular fluid. In some cases a large part of the loss of extracellular sodium was explained by transfer of sodium from the extracellular to the intracellular fluids. Such a transfer of sodium explained the acidosis in 1 case. In other cases sodium was lost from the intracellular as well as from the extracellular fluids.

Loss of intracellular potassium was a prominent feature of all cases and was equivalent in 2 cases to about one fourth of the estimated normal potassium content of the body. This loss of potassium was in excess of the loss which would be expected from loss of nitrogen.

No great disturbance in the relative concentration of intracellular phosphorus was demonstrated.

The usual replacement therapy of fasting and the parenteral administration of solutions containing sodium chloride, sodium lactate and dextrose corrected the extracellular concentrations. However, considerable sodium entered the cells in 2 cases, and the loss of potassium was aggravated.

Replacement of intracellular potassium was obtained by adding 1 to 2 Gm. of potassium chloride to submaintenance feedings. One observation indicated that replacement of intracellular potassium is not likely to occur if the diarrhea continues and submaintenance milk feedings without added potassium chloride are given. The data indicate that the usual milk mixtures contain sufficient potassium to replenish the tissues if these mixtures can be taken in the amounts necessary for growth.

During the period of fasting, retention of intracellular potassium can be produced by adding potassium chloride to solutions containing sodium chloride and sodium lactate. Such treatment restores extracellular concentrations and replaces the deficit of potassium in part. Accompanying this replenishment of both intracellular and extracellular electrolyte, the baby looked better than after the usual type of treatment and recovered from attacks of diarrhea that would usually be fatal.

The significance of deficit of potassium is discussed.

FROM THE AUTHOR'S ABSTRACT.

HYPERPLASIA OF GUMS WITH EPANUTIN [DIPHENYLHYDANTOIN SODIUM U. S. P.] THERAPY: TWO CASES. A. I. DATE, Proc. Roy. Soc. Med. **38**:567 (August) 1945.

The 2 patients, boys, were given equal doses of diphenylhydantoin sodium ("epanutin"; "dilantin"), 1½ grains (0.097 Gm.), three times a day, combined with phenobarbital. Both patients showed an overgrowth of gum tissue, which appeared to be true hyperplasia (not hypertrophy); as it has not occurred in edentulous patients, this hyperplasia is thought to arise in the periodontal tissue. It would appear to be a toxic manifestation. Other toxic symptoms reported in patients treated with diphenylhydantoin were absent. The hyperplasia must, of course, be differentiated from other conditions causing generalized swelling of the gums.

WILLIAMSON, New Orleans.

Nervous Diseases

THE PETIT MAL EPILEPSIES: THEIR TREATMENT WITH TRIDIONE (TRIMETHADIONE N. N. R.). WILLIAM G. LENNOX, J. A. M. A. **129**:1069 (Dec. 15) 1945.

Petit mal epilepsy, or pyknoepilepsy, is characterized clinically by lapses of consciousness for five to thirty seconds, and electroencephalographically by alternate spike and wave patterns. Myoclonic epilepsy causes single contractions of the flexor muscles and may be associated with a coinciding dart and dome pattern on the electroencephalogram. Akinetic epilepsy is characterized by loss of postural control with resultant head nodding or falling. The electroencephalogram may show many abnormalities, including the dart and dome pattern.

None of these seizures responds well to the usual anticonvulsant medications. A new medicament, trimethadione ("tridione" or 3,5,5-trimethyloxazolidine-2,4-dione), was given to 50 patients subject to these types of seizures. The dose was 1 to 2 Gm. daily. The seizures ceased in 28 per cent of the cases, were reduced to less than one-fourth their previous number in 52 per cent and were but little affected in 20 per cent in a series of observations extending over a period of fifteen months. The chief side effect was photophobia, which occurred more commonly in the older children and in adults.

Grand mal seizures were not influenced by administration of the drug, but were even increased in number.

In some patients the seizures, which stopped while the patient was taking trimethadione, did not recur after medication was discontinued.

BAIRD, Wauwatosa, Wis.

COPPER CONTENT OF THE CEREBROSPINAL FLUID. STEN AXTRUP, Ann. paediat. **166**:259 (May) 1946.

The copper content of the cerebrospinal fluid was determined in various disease states and proved to be low, about 15 per cent. The variations were not great. The highest measured value was 26 per cent; the lowest, 1 per cent. Contrary to expectation, the copper content of the cerebrospinal fluid in cases of meningeal infection was relatively low.

FROM THE AUTHOR'S ABSTRACT.

Psychology and Psychiatry

THE NATURE OF TRANSIENT OUTBURSTS IN THE ELECTROENCEPHALOGRAM OF EPILEPTICS. DENIS WILLIAMS, Brain **67**:10, 1944.

Williams states that the electroencephalogram of epileptic patients during seizures is always abnormal, while the interseizure records may be either normal or abnormal. When abnormal, the record may be nonspecific, but an episode seizure discharge may be superimposed. Williams investigated the relation between the appearance of episodic discharges in the electroencephalogram and the liability of the patient to epileptic attacks. A patient who had had one definite and one questionable grand mal seizure was found to have spontaneous larval petit mal discharges. It was observed that closure of the eyes produced similar electrical disturbances. During alterations in the p_H and the gaseous tension of the blood, the reflex disturbances behaved in the same way as do spontaneous wave and spike formations. The efficiency of the trigger mechanism, closure of the eyes, was not affected. Williams concluded that in this instance even the smallest paroxysmal outburst represented abnormal cerebral activity of an epileptic nature.

The electroencephalograms of epileptic patients, normal controls, neurotic persons and patients with head injuries were studied and classified as normal or abnormal, and the abnormal records were further classified as (*a*) not specifically epileptic, (*b*) containing larval epileptic outbursts or (*c*) containing other paroxysmal outbursts. Larval epileptic outbursts included high voltage, abnormal activity with sudden onset and cessation, conforming to the described types of organized patterns. Other paroxysmal outbursts included all other types of transitory disturbances, such as are usually associated with epilepsy but are not well enough defined to be considered larval epileptic attacks. Williams found that abnormal electroencephalograms were six times as common in epileptic patients as in normal controls; larval epileptic disturbances occurred in more than 25 per cent of epileptic patients but did not occur in nonepileptic subjects; paroxysmal outbursts, both larval and others, occurred in 56 per cent of epileptic patients but in only 0.5 per cent of nonepileptic

subjects, and paroxysmal outbursts occurred thirty times as frequently in patients with head injuries as in nonepileptic subjects and were more common after penetrating wounds.

Williams studied a group of patients with states frequently associated with epilepsy. This group was divided into patients with a constitutional and those with a symptomatic epileptic tendency. Patients with a constitutional epileptic tendency included (*a*) twins both of whom presented paroxysms of wave and spike activity in their electroencephalograms, but only one of whom had clinical seizures, and (*b*) a patient whose only seizure resulted from the oral administration of a small dose of camphor and who presented in his record paroxysmal disturbances suggesting epilepsy. These disturbances were still present three and a half months after the administration of the camphor and hence were considered indicative of a convulsive tendency.

Patients with a symptomatic epileptic tendency included (*a*) persons with paroxysmal outbursts without overt seizure (a patient with glioma of the right hemisphere, a patient with bilateral atrophy of the frontal lobe, a patient with osteomyelitis of the occipital bone and 3 patients with head injury) and (*b*) patients with paroxysmal outbursts following open or closed head injury and subsequently overt seizures.

From these results, Williams concludes that the presence of paroxysmal disturbances in the electroencephalogram of an epileptic patient or of one suspected of having epilepsy can be considered reliable supporting evidence for the diagnosis of epilepsy. Nonspecific and nonepisodic changes cannot be so construed. The presence of paroxysmal changes in the electroencephalogram in cases of known cerebral disease, such as neurosyphilis, should not be considered as invalidating the use of the presence of such outbursts as confirming the diagnosis of epilepsy, but, instead, should be considered as evidence of a serious liability of the patient with cerebral disease to the development of epilepsy. Thus, the old clinical concept of latent and active epilepsy is supported by the correlation of clinical and electroencephalographic data.

FORSTER, Philadelphia. [ARCH. NEUROL. & PSYCHIAT.]

SYMPTOMATOLOGY OF AMAUROTIC FAMILIAL IDIOCY. E. NASSAU, Ann. paediat. **166**:265 (May) 1946.

In 4 young patients with Tay-Sachs disease (infantile amaurotic familial idiocy) the long bones contained fatty marrow with few cells, instead of the normal marrow with a high number of cells. The marrow in the flat bones was normal and contained many cells. These observations support the view that the process of degeneration in amaurotic familial idiocy affects not only the central nervous system but also the other organs. This seems to justify the claim that Tay-Sachs disease should be counted among the so-called storage diseases.

FROM THE AUTHOR'S ABSTRACT.

Diseases of the Muscles, Bones, Joints and Lymph Glands

OSTEOMYELITIS IN INFANTS. ROBERT A. J. EINSTEIN and COLIN G. THOMAS JR., Am. J. Roentgenol. **55**:299 (March) 1946.

Ten cases of osteomyelitis in infants under 6 months of age are presented, and the peculiarities of the disease in this age group are emphasized. Hemolytic streptococcus is the most frequent causative organism; Staphylococcus aureus is the next commonest cause. It is usually a blood-borne disease. The original foci

are thought to be diseases of the respiratory tract and umbilical and cutaneous infections.

The anatomic factors which influence the disease in infants are the spongy texture of the bone, the large vascular spaces and the thin cortex. Usually the infection passes through the cortex to the subperiosteal space, rather than into the shaft of the bone. Destruction of bone is minimal and sequestration is rare. Early there is elevation of the periosteum, which may rupture and form soft tissue abscesses. Pyarthrosis is a common and most serious complication. It is usually effected in one of two ways: 1. Infection may spread from the metaphysis through the adjoining epiphysial cartilage and epiphysis into the joint. 2. In joints in which both the epiphysial cartilage and part of the metaphysis are within the joint capsule, the infection may break through the periosteum to reach the joint.

The onset is usually gradual with minimal systemic manifestations. The complaint is swelling and loss of function of the part. In occasional cases the bacteremia persists and the acute onset with severe systemic symptoms characteristic of the course in older children is seen. Recovery in these cases is uncommon. With proper treatment and absence of complications healing occurs in three to eight weeks. Immobilization, hydration, antianemia therapy, chemotherapy, surgical drainage of subperiosteal and soft tissue abscesses and general supportive measures are essential. The mortality rate varies with the incidence of septicemia.

The authors point out that, because of the usually benign course, roentgenograms of the early stages are rarely obtained. They discuss the various roentgenographic findings during the course of the disease.

The age of transition from the infantile course to that of the older age groups has not been established.

HARRISON, Chicago.

Skin Diseases; Allergy

HAPAMINE [A HISTAMINE AZOPROTEIN] IN THE TREATMENT OF ALLERGIC RHINITIS IN CHILDREN. HOWARD L. EDER, Arch. Pediat. **63**:209 (May) 1946.

The author discusses his experiences in the handling of allergies in children generally. He then discusses briefly some rather remarkable therapeutic results obtained from the giving of injections of "Hapamine" (a histamine azoprotein substance). The discussion is not supported by any laboratory determinations or other objective findings. Reference is made to similar remarkable results in fourteen additional patients in the author's experience. No bibliography is given.

GRULEE JR., Minneapolis.

THE ANTI-HISTAMINE PROPERTIES OF BENADRYL, β-DIMETHYLAMINOETHYL BENZOHYDRYL ETHER HYDROCHLORIDE [DIPHENHYDRAMINE HYDROCHLORIDE]. EARL R. LOEW, ROBERT MACMILLAN and MARGARET E. KAISER, J. Pharmacol. & Exper. Therap. **86**:229 (March) 1946.

In experimental animals the drug acted as an antispasmodic against histamines on intestinal muscle in exceedingly high dilutions (1:50,000,000), but much larger doses were required to act against acetylchlorides and barium. It is probably this action that led to its clinical use in relieving infantile pyloric obstruction, but its effectiveness would seem to be limited. Other experimental results are also reported.

PILCHER, Cleveland.

SYMMETRIC GANGRENE OF THE EXTREMITIES (RAYNAUD'S DISEASE). MARIO SACCA, Pediatria **54**:117, 1946.

The author presents the clinical picture of Raynaud's disease and describes the case of an 11 month old infant which was unusual with respect to the age of the patient, the localization (feet) and the clinical course.

FROM THE AUTHOR'S ABSTRACT.

Miscellaneous

ACTIVITIES OF THE MOSCOW PEDIATRIC SOCIETY DURING THE SECOND WORLD WAR: SOCIETY TRANSACTIONS. B. I. MOLCHANOV, Pediatriya **3**:71 (March) 1943.

It is reported by the author that in wartime, during the periods from June 1941 to January 1943, the Moscow Pediatric Society had continued almost uninterruptedly its various scientific activities. The various pediatric problems created by the wartime conditions constituted the main themes for the society's regular and special sessions.

The subjects of current interest, as judged by the papers most commonly presented at the meetings of the society, were as follows: (1) acute infectious diseases: diphtheria, typhus, measles and typhoid; (2) tuberculosis, and (3) nutritional disturbances and avitaminoses: nutritional edema, rickets, scurvy, etc.

The research work conducted by the various scientific commissions of the Moscow Pediatric Society was temporarily interrupted by the acute war emergencies, but was resumed in March of 1942. The following scientific commissions presented their reports at subsequent meetings: (1) Childhood Tuberculosis (I. E. Maisel, president), (2) Physiology and Pathology of the Newborn (I. A. Stern, president), (3) Digestive and Nutritional Disturbances (N. I. Langovoy, president), and (4) Acute Infectious Diseases (V. I. Molchanov, president). The specific problems of investigation by the various members of these commissions are enumerated.

BODER, Los Angeles.

PHYSIOLOGIC SYMPTOMS AND THERAPEUTIC PROCEDURES IN EXTREMELY LOW BODY TEMPERATURE. J. JONGBLOED, Nederl. tijdschr. v. geneesk. **89**:351 (Nov. 17) 1945.

The author, physiologist at the university of Utrecht, discusses what must be regarded as the most logical therapy in cases of extremely low body temperatures; such cases occurred rather frequently in Holland, especially among babies, during the cold period of the winter of 1944-1945.

The principal factor for maintaining the temperature of the central part of the body in cases of cooling is an increased metabolism. When cooling increases, this mechanism no longer can operate, and then also the temperature of the center of the body falls. This causes a decrease in the temperature of the blood, and as a result the compound oxyhemoglobin can be released from the tissues only with difficulty. The stimulated metabolism under these circumstances can have no effect and the production of heat decreases. No doubt death caused by cooling is a consequence of a shortage of oxygen, notwithstanding the fact that the blood is rich in oxygen (attached to hemoglobin). Thus in a cooled subject one has to deal in the first place with a low body temperature, relative shortage of oxygen and, besides these, a shortage of food. The latter is caused by an increased metabolism and for the greater part by an insufficient intake of food.

As regards the therapy, the supply of heat from the outside to a certain degree is irrational. The most important point is to increase the production of heat in

the center of the body. Therefore the author recommends injections of solutions of dextrose and inhalation of oxygen (tent or mask). When possible active and passive movements of the extremities are favorable.

VAN CREVELD. Amsterdam, Netherlands.

HYPOTHERMIA WITH TOTAL COURSE DURING THE WINTER OF 1945. A. DE MINJER, Nederl. tidjschr. v. geneesk. **90**:200 (March 16) 1946.

During the cold months of 1945 the author observed a number of extremely underfed patients, who all had as the most important symptom a low body temperature. They all died shortly after the arrival at the clinic, notwithstanding all care taken of them. The autopsy showed that the hypothermia arose in different ways. One group of patients had suffered severely from hunger and cold; these persons at autopsy proved to be emaciated, but they had no important changes in the organs. No glycogen could be demonstrated in their organs. Here the hypothermia must have been caused by a lack of glucose for combustion.

In three other groups of patients the liver contained an important amount of glycogen, while the autopsy took place a long time after death; sometimes also much glycogen was present in the skeletal muscles. It appeared in a number of cases belonging to one of the latter groups that the structure of the thyroid gland had completely changed. In a number of children with hypothermia this structure closely resembled the structure of the thyroid gland in newborn children and animals.

In 1 child with hypothermia severe anemia and extensive fatty degeneration of the parenchymatous organs were observed, pointing to the disturbed cell metabolism.

Some therapeutic conclusions are drawn from the observations in these cases.

VAN CREVELD, Amsterdam, Netherlands.

EXTREMELY LOW BODILY TEMPERATURES IN BABIES. A. L. VELDKAMP, Nederl. tijdschr. v. geneesk. **90**:209 (March 16) 1946.

The author treated a number of babies who were taken into the clinic with an extremely low bodily temperature according to the therapeutic rules indicated by Jongbloed (1945). Care was therefore taken to obtain a slow rise in temperature, without application of too much heat from the outside, with continuous application of oxygen and with injections of dextrose. Together with these measures stimulating drugs (e. g., epinephrine) were administered. With a single exception the results of this mode of treatment were not more successful than of treatments used formerly.

VAN CREVELD, Amsterdam, Netherlands.

IMPROVED METHOD FOR INVESTIGATION OF PUS. W. J. QUARLES VAN UFFORD, Nederl. tijdschr. v. geneesk. **90**:288 (April 13) 1946.

In investigating different kinds of pus the author repeatedly had to deal with the difficulty that the pus was dried or so coagulated that the smoothing of the pus on an object slide or on a culture medium was difficult. Therefore he made use of a method recommended by Massini (1943), i. e., addition of 0.76 per cent of sodium citrate to the exudate directly after the withdrawal. To reach this concentration 1 part of 3.8 per cent sterile sodium citrate was always added to 4 parts of the exudate. This addition of sodium citrate greatly facilitated the bacteriologic examination.

VAN CREVELD, Amsterdam, Netherlands.

Society Transactions

AMERICAN ACADEMY OF PEDIATRICS

J. I. Durand, M.D., President

National Meeting, Pittsburgh, Feb. 24-27, 1947

ROUND TABLE DISCUSSIONS

I. Sepsis in the Newborn

Sepsis in the Newborn. Dr. A. H. PARMELEE, Oak Park, Ill.

The problems of the newborn have been discussed on previous occasions in these round table discussions, in which the major hazards of this transition period have been covered thoroughly. Most of the disturbances of current popular interest, such as the hemolytic diseases, the hemorrhagic diseases and epidemic diarrhea, have likewise been rather adequately covered in recent years. There remains a subject which of late has been neglected, namely, sepsis, to which I invite your attention. This is a disease to which the pediatricians and obstetricians of the past were compelled to give a great deal of attention, but now, thanks to the general excellence of aseptic technic in the delivery room and the improvements in the care of the newborn, it is relatively rarely seen. This disease, however, still takes its toll, and neonatal mortality statistics show that deaths from infectious causes continue to be too frequent to justify complacency.

The choice of this subject was stimulated by a realization that residents in pediatrics and in obstetrics would rarely consider the possibility of sepsis when confronted with a sick newborn infant unless it were suggested to them by an experienced attending physician. This fact I take as evidence that in their medical education the subject has received scant attention. I believe that it was not pure coincidence that Dr. S. H. Clifford, Brookline, Mass., chose "Infections of the Newborn" for the subject of his round table discussion, but that his choice was significant of a mutual consciousness among men in the field of pediatrics that the hazard of infection still lurks in the delivery room and in the maternity nursery and that they must be alert to recognize its varied manifestations and the implications as regards the technic of prevention.

The term sepsis will be considered in this discussion as meaning a systemic infection due to invasion of the blood stream by pyogenic bacteria. In some cases blood cultures will yield organisms, and in others metastatic infections of various organs will be obvious evidence that the infection was blood borne.

The newborn is peculiarly vulnerable to infections with pyogenic bacteria for several reasons. First, there are unusually favorable portals for entrance of pyogenic organisms. For example, the umbilical stump is a fresh, open wound; the skin is tender and readily abraded and traumatized, even from the handling incident to necessary care; the mucous membranes of the mouth are frequently traumatized during measures for resuscitation; the lungs offer an especially favorable culture medium for bacterial growth when asphyxia and areas of atelectasis persist, and the gastrointestinal tract is also an atrium for infection through ingestion of contaminated material. Second, the newborn possesses little resistance to pyogenic bacteria, either by passive transfer of antibodies through the placenta or through ability to manufacture specific antibodies. Some pneumococcic, strepto-

coccic and staphylococcic antibodies have been demonstrated in fairly high concentrations in the newborn, but they disappear abruptly in a short time. These antibodies are apparently antitoxic rather than bactericidal, at least as regards the Staphylococcus, and this fact may account for the surprising lack of toxic symptoms in some cases of early staphylococcic sepsis. Third, there are certain physiologic characteristics of the skin, the subcutaneous fat, the bones, and probably other tissues that cause them to react differently to irritants and to injuries than they would in later life. The skin of the newborn, for example, exhibits a peculiar tendency to epidermolysis which is not present in any other period of life; the subcutaneous fat has a unique reaction to trauma, in which there occur areas of induration characterized by the presence of large collections of fatty acid crystals, constituting a noninfectious inflammatory reaction, which is called traumatic subcutaneous fat necrosis (adiponecrosis neonatorum), and the sites of endochondral ossification in the bones are especially sensitive to bacterial toxins and other noxae.

It is concerning these peculiarities that pediatricians must become better informed in order adequately to appraise the dangers of infection in the newborn and to understand the clinical course of a generalized infection or sepsis. The following cases observed in the Cook County Hospital during the past four years illustrate many of the characteristics of sepsis of the newborn.

REPORT OF CASES

CASE 1.—M. B., a premature infant, weighing 3 pounds 1 ounce (1,389 Gm.) at birth, presented cellulitis on the back on the tenth day; pronounced fluctuations in temperature, from 97 to 102 F., and intense icterus on the seventeenth day. Blood was present in the stools at various times from the twenty-first to the forty-ninth day. Cellulitis developed on the left thigh on the fiftieth day, with abscess formation. The temperature was normal after the sixty-seventh day. The icterus faded; no more abscesses developed, and progress was normal. The patient was discharged at the age of 4 months and 3 days, weighing 5 pounds 1 ounce (2,296 Gm.). Treatment had consisted of administration of sulfathiazole and penicillin, blood transfusions and breast milk feedings. No blood cultures were made. Pus from the abscesses yielded Staphylococcus albus on culture.

CASE 2.—J. G., a full term infant, born of a normal delivery, whose condition at birth was good, weighed 7 pounds 6 ounces (3,345 Gm.) at birth. On the fifth day, the child nursed poorly and was irritable; the temperature was 102 F.; the fontanel bulged; the legs were strongly flexed, but there were no other symptoms. Examination of the spinal fluid showed 1,000 cells per cubic millimeter, most of which were polymorphonuclear leukocytes. Culture of the spinal fluid yielded Bacillus coli. There was leukocytosis with a count of 30,000. The blood cultures also yielded B. coli. Treatment consisted of administration of sulfathiazole and blood transfusions. Subsequent blood cultures yielded no pathogens. The patient recovered, but with hydrocephalus and mental deficiency.

CASE 3.—C. B. W., a full term infant, whose delivery was normal and condition at birth good, weighed 7 pounds 11¼ ounces (3,508 Gm.) at birth. On the fifth day the temperature was 105 F.; icterus was prominent, and the child was listless and apathetic, looked toxic and refused to nurse. There was a foul-smelling, purulent discharge from the umbilical stump. Treatment consisted of administration of sulfamerazine and a blood transfusion. The child died on the sixth day. Autopsy showed omphalitis, thrombophlebitis of the umbilical vein and parenchymatous degeneration of the liver.

CASE 4.—J. J., a full term girl whose delivery was normal and condition at birth good, weighed 6 pounds 8 ounces (2,948 Gm.) at birth. The initial examination during the first day of life revealed no abnormality. On the sixth day the temperature was 102 F., but the child's condition was good and no cause for the rise in temperature could be found. Physical examination revealed nothing abnormal except for a slight distention of the abdomen. On the eighth day the child was listless and refused food but had no fever. There was a tendency to opisthotonos, and the fontanel was sunken rather than bulging. A spinal tap yielded grossly purulent fluid, with a cell count of 16,000, mostly polymorphonuclear leukocytes. Cultures yielded B. coli. Sulfadiazine was given, and the response was rapid. The infant nursed well again and on the eleventh day the weight was 1½ ounces (43 Gm.) over that at birth. Administration of sulfadiazine was continued for fourteen days. On the twenty-seventh day signs of intestinal obstruction developed. A laparotomy revealed kinking of the bowel, due to extensive adhesions from an earlier peritonitis. An anastomosis of the ileum was made. Recovery was good, and the infant seemed to be doing well until nearly four weeks after the operation, when she died suddenly, at the age of 54 days. Autopsy revealed conspicuous anemia of the myocardium, with dilatation of the left ventricle; intense pulmonary congestion; chronic focal meningitis, and chronic fibrinous peritonitis with adhesions between all loops of the bowel. Cultures of the spleen and of cerebrospinal fluid taken from the lateral ventricles yielded B. coli.

It seems probable that the meningitis and the peritonitis occurred concomitantly, but with no clinical evidence of the peritonitis until the symptoms of intestinal obstruction appeared. A further point of interest is that the mother had persistent diarrhea during her entire stay in the hospital. One might suspect that she was the source of the infection. An interesting point regarding immunity arises in consideration of this case, since the child was breast fed for more than two weeks. The colostrum and later milk were unable to protect the baby from infection with the colon bacillus. It will be recalled that Theobald Smith demonstrated that an immunity in newborn calves to colon bacillus infection was acquired with their first feedings. Toomey showed also that agglutinins for the colon bacillus are present in greater strength in colostrum and the later milk than in the infant's serum at birth.

CASE 5.—N. H., a full term boy, whose delivery was normal, condition good, weighed 6 pounds 5½ ounces (2,878 Gm.) at birth. Initial physical examination on the first day revealed nothing abnormal. On the ninth day there was a fluctuant swelling over the costochondral junction of the left sixth rib. The following day a small reddened area appeared over the proximal end of the right tibia, which was tender and, after a few hours, fluctuant. There was now for the first time a slight elevation of temperature, to 100.2 F., but the infant did not appear sick. On the following day the distal end of the right femur was considerably swollen. A diagnosis of osteomyelitis was made, and treatment with penicillin was started. No evidence of change in bone could be demonstrated by roentgenographic examination at this time. The temperature subsided immediately and the infant took food well and did not seem sick. On the twenty-first day a roentgenogram showed osteomyelitis of the distal end of the right femur and of the proximal end of the right tibia. Direct smears of pus obtained by aspiration of the swellings over the rib and the tibia showed gram-positive cocci, and cultures of the material yielded Staphylococcus aureus. On the twenty-sixth day a large swelling developed at the proximal end of the right humerus, which shortly became fluctuant. Cultures of blood taken before administration of penicillin was started yielded Staph. aureus.

The child is now 7 weeks old and is making good progress. The entire clinical course has been afebrile and asymptomatic except for two days at the onset of the infection, when he had a slight fever. There was no obvious portal of infection. [Slides.]

CASE 6.—F. M. was born at or near term, of a normal delivery. The condition at birth was good. The weight at birth was 5 pounds 8 ounces (2,495 Gm.). Routine examination on the second day of life revealed nothing abnormal. On the fourth day there was frequent emesis of bile-stained mucus and food. Meconium had been passed normally, and the stools were of brownish green fecal material. The temperature that evening was 101 F.; the abdomen was distended; respirations were grunting, and there was decided retraction of the sternum and the costal margins. There was general rigidity of the body, and the color was gray. There was no bulging of the fontanel. The following day the temperature was 102 F. and the child died, at the age of 5 days.

The diagnoses considered were (1) volvulus; (2) atelectasis, and (3) pneumonia.

Autopsy revealed purulent meningitis and bilateral bronchopneumonia. A culture of the cerebrospinal fluid yielded B. coli.

In this case there were no symptoms of meningitis, and the febrile reaction was mild. The only symptoms were vomiting, dyspnea, fever and toxemia.

CASE 7.—D. B. was a full term infant, born of a normal delivery. The condition at birth was good. The weight at birth was not recorded. On the sixth day the infant vomited and had a temperature of 101.6 F. The abdomen was distended, and the child looked sick. During the next two days the baby had watery stools, refused to nurse and was apathetic. The infant died on the ninth day. No diagnosis was made. Autopsy showed diffuse fibrinopurulent peritonitis, purulent omphalitis, dilatation of the ventricles of the heart, parenchymatous degeneration of the liver and septic splenitis. Neither arteritis nor phlebitis was mentioned in the autopsy report.

CASE 8.—E. S. was a full term girl, the product of a difficult breech delivery after a prolonged labor. The mother was febrile at the time of labor. Her condition was described as intrapartum sepsis. The infant's condition at birth was poor. She did not breathe spontaneously and was resuscitated with difficulty. A tracheal catheter was used, and she was given oxygen. A vitamin K preparation and nikethamide were administered, and she was placed under treatment with sulfathiazole, 1 grain every four hours, which is routine procedure after resuscitation with the tracheal catheter.

The weight at birth was 8 pounds 11½ ounces (3,955 Gm.). Physical examination twenty-four hours after birth showed the posture characteristic of breech presentation and delivery. The general condition was fair, the cry strong and the Moro reflex present but incomplete. There were an abrasion on the left buttock and an area of traumatic subcutaneous fat necrosis near by. On the fourth day there were areas of subcutaneous fat necrosis on the thighs, back and pectoral region and at the nape of the neck. On the tenth day fluctuation developed in one area of subcutaneous fat necrosis on each thigh, and for the first time an elevation in temperature was noted. The child's general condition remained good. During the next nine days there was mild fever, with a temperature of 100 to 100.8 F. One fluctuant area ruptured spontaneously and discharged characteristic liquefied fat and debris. At this time, also, icterus appeared and rapidly became more intense. The temperature became normal on the twenty-fifth day, but the general condition deteriorated rapidly in spite of penicillin and sulfadiazine therapy. Cultures of pus aspirated from fluctuant areas yielded Staph. aureus. Biopsy of

one area of induration made on the twenty-third day showed the changes characteristic of idiopathic fat necrosis in the subcutaneous fat. Death occurred on the thirty-second day. Autopsy revealed subcutaneous fat necrosis on the buttocks, thighs, back, neck and arms; an ulcerated necrotic area on the buttocks; icterus; mucopurulent tracheobronchitis, and foci of atelectasis in both lungs.

This case illustrates how the tendency in the newborn to development of areas of subcutaneous fat necrosis from trauma incident to birth constitutes a hazard to life by offering a site for invasion of pyogenic organisms.

[Slides.]

CASE 9.—M. M., a full term girl, born of normal delivery, whose condition at birth was good, weighed 8 pounds, 10½ ounces (3,926 Gm.) at birth. There was no complaint until the ninth day, when the infant seemed apathetic, nursed poorly and had fever, the temperature reaching 102.2 F. by the twelfth day. The weight was then only 8 pounds ¾ ounce (3,650 Gm.). Physical examination on that day revealed nothing abnormal except for absence of the Moro reflex, general apathy and fever. Examination of the spinal fluid showed it to be normal. The following day there was a swelling in front of the left ear, which rapidly increased in size and became reddened, and there appeared some purulent discharge in the left external auditory canal. The opening of Stensen's duct on that side was inflamed, and on the sixteenth day it was apparent that there was acute suppurative sialadenitis of the parotid gland, with pus discharging through a point of spontaneous rupture into the external auditory canal. A culture of pus aspirated from the abscess of the parotid gland yielded Staph. aureus.

The next day there were a fluctuant swelling on the left index finger and a red, swollen area on the right little finger. A day later there was dulness over the lower lobes of both lungs, especially the right, and moist rales were heard on the right side. A diagnosis of sepsis with multiple metastatic foci was made. Within the next few days there appeared enlargement of the left axillary lymph nodes, a swelling over the left scapular area, and another over the distal end of the right fifth rib. An incision of the fluctuant area over the left scapula on the twenty-ninth day permitted evacuation of the pus from the purulent axillary lymph nodes as well, revealing extensive communicating abscesses. Roentgenographic examination of the left shoulder at this time showed osteomyelitis of the left scapula. Osteomyelitis of the right fifth rib was also demonstrated. A blood culture made on the fortieth day yielded Staph. aureus. The infant received sulfonamide therapy, but a blood level for the drug above 5.5 mg. per hundred cubic centimeters for some reason could not be attained.

At the age of 3 months the general condition was good. The child was afebrile most of the time, except for short periods when the pulmonary infection showed exacerbations. She remained in the hospital until she was 14 months old. There were occasional new abscesses, with extrusion of sequestrums from the various areas of osteomyelitis, and now and then exacerbations of the pulmonary infection, but her condition on discharge was relatively good. Blood cultures usually yielded no organisms, but as late as the sixth month one was positive for Staph. aureus.

One year later she was readmitted because of bronchopneumonia. She died after three weeks, at the age of 26 months.

Autopsy revealed mucopurulent bronchitis; diffuse saccular bronchiectasis; extensive foci of atelectasis in all pulmonary lobes; pleural adhesions on the right side and several foci of chronic osteomyelitis.

Sepsis was due to a staphylococcic, metastatic infection of the bones and lungs with a chronic course. The portal of entry was the parotid gland.

[Slides.]

CASE 10.—P. W., a full term infant of normal delivery, whose condition at birth was good, weighed 5 pounds 10½ ounces (2,566 Gm.). On the sixth day the child developed cellulitis of the abdominal wall which extended downward from the umbilicus to the pubis. The umbilical stump was inflamed, and there was some purulent drainage from it. The temperature was 102 F., and remained at about that level for two days, after which it fell by lysis and was normal on the eleventh day of life. There was slight diarrhea during the first days of the infection. No blood cultures were made. Treatment was with penicillin and sulfanilamide.

This infection obviously originated in the umbilical stump and extended as a periarteritis along the umbilical arteries, with early symptoms of sepsis. The progress of this infection was dramatically checked by the therapeutic weapons now available.

Of these 10 cases of sepsis, the portal of infection was the umbilicus in 3, traumatized subcutaneous fatty areolar tissue in 2 and a salivary gland in 1, and in 4 it was undetermined. There was metastatic spread to the meninges in 3 cases, to the peritoneum in 2 cases (in 1 case both the peritoneum and the meninges were involved, probably simultaneously) and to the bones in 2. The lungs were infected in 3 cases, as well as other tissues, but whether this was from metastatic spread of the infection or from direct infection of the air passages could not be certainly determined.

The causative organism was definitely, or presumptively, determined in 7 cases and undetermined in 3. The organism was Staph. aureus in 4 cases and B. coli in 3 cases.

In all cases in which meningitis occurred, B. coli was the infective organism, whereas in both cases of osteomyelitis the agent was Staph. aureus. In 1 of the 2 cases of peritonitis, B. coli was present, and in the other the causative organism was not determined.

These illustrative cases taken from clinical material in the last four years demonstrate only a few of the sources of infection. Several others can be mentioned, such as tooth bud infections with osteomyelitis of the maxilla or mandible; perforation of the intestine due to obstruction from volvulus or meconium ileus with peritonitis; superficial infections of the skin followed by multiple cutaneous abscesses and general sepsis; infections of the lungs, and otitis media with extension to the meninges.

It is important to remember that the diagnosis of sepsis in the newborn is difficult to make because symptoms may be almost entirely lacking. Fever may be the only symptom at first, and even this may be slight or altogether lacking. When a newborn child who has previously been doing well suddenly becomes apathetic, nurses poorly and loses weight, one should become suspicious, especially if careful physical examination and a check on the nurse's record give no clue. On several occasions, when my colleagues and I were confronted with this picture, a spinal tap has disclosed meningitis or a blood culture has been diagnostic. But in some other instances no diagnosis, or a wrong one, has been made and peritonitis has been encountered at autopsy. The symptoms can be misleading; vomiting, diarrhea, convulsions, severe icterus, melena, ecchymoses and petechia, in varying combinations, or singly, may appear to cloud the picture.

I hope that the discussion on this paper will be free and informal. I hope it will not turn out to be just "an experience meeting," but of course, well chosen cases to illustrate pertinent points are in order. I should like particularly to get help from the other members of the round table in clearing up such problems as are related to immunity, or to the lack of it, in the newborn, the physiologic

peculiarities of the newborn which determine the nature of his response to infection and the manner in which such infection spreads, why certain tissues are so prone to involvement in metastatic spread, and other similar questions. Reports of experience with the newer methods of treatment are also in order.

DISCUSSION

DR. E. L. PIPER, Pittsburgh: You will notice that most of these cases have been those of premature or immature infants. The importance of maintaining a correct body temperature is recognized, and I wonder whether lack of consideration of this point could have an influence on the development of infections such as these. On delivery and immediately thereafter the maintenance of an adequate body temperature in the newborn baby should be insured by special nurses in the delivery room and the nursery.

DR. A. H. PARMELEE, Oak Park, Ill.: Dr. Piper is quite right. My associates and I routinely send all babies weighing less than 5 pounds (2,268 Gm.) to the station for premature infants. Infants weighing from 5 to 6 pounds (2,268 to 2,722 Gm.) are kept in a special nursery in heated cribs.

DR. J. C. JAUDON, St. Louis: It is obvious that a few full term and many premature infants appear to live in symbiosis with invading pathogenic organisms for many hours, or even days, before there is clinical evidence of sepsis. In an effort to explain this lack of resistance, or of antibody response, I am constantly reminded of clinical and experimental studies that have substantiated the theory of physiologic hypofunction of the adrenal cortex during early life. The poorly developed defense mechanism of the newborn may be just another manifestation of low function of the adrenal cortex. It is generally known that patients with adrenal cortical hypofunction (Addison's disease) and hypopituitary cachexia (Simmonds' disease) are highly susceptible to infections. These patients have a relative and actual increase in the number of lymphocytes circulating in the blood stream. In this and in other respects they are similar to premature and newborn infants. Dougherty and White (Functional Alterations in Lymphoid Tissue Induced by Adrenal Cortical Secretion, *Am. J. Anat.* **77**:81-116 [July] 1945) have shown that in adrenalectomized animals the blood count shifts to the right and there is an accompanying lowering of the total plasma proteins, which is almost entirely due to a reduction of the gamma fraction of the globulin. These investigators, and others, have also adequately demonstrated that the lymphocytes are mainly responsible for the storage of the gamma globulin fraction in the reticuloendothelial system. After administration of sufficient replacement hormone, the blood count and the immune globulin return to normal in these animals. Adequate storage of this antibody-containing globulin in the reticuloendothelial system apparently plays an important part in tissue resistance. The high percentage of lymphocytes in the blood and the low serum globulin, which is characteristic of all premature infants during early life, may partly explain the physiologically low resistance to infections in these infants.

Administration of immune globulin has failed to increase the defense mechanism against the ordinary bacterial infections. This globulin cannot be stored in the reticuloendothelial system without the presence of adequate amounts of circulating C_{11} (sugar hormone) steroids. If there are small amounts or an absence of the steroid during this period of life, the parenteral injections of immune globulin could not be stored in the body but would most likely be utilized as food.

My colleagues and I anticipate carrying out clinical investigations in an effort to correlate the change in the blood picture with such factors as the fluctuations of

the globulin fraction of the total proteins following the simultaneous injection of immune (human) globulin and C_{21} steroid. Other factors, such as an immature liver, may also play an important role in this vital problem; however, I feel that the suggested study offers a promising outlook in an attempt to explain in part the physiologic handicaps responsible for the lack of specific tissue resistance during the early period of life.

DR. A. H. PARMELEE, Oak Park, Ill.: Dr. Jaudon's remarks on the role of the adrenal glands are interesting. Hemorrhages into the adrenal glands or infections of the adrenal cortex may be of importance in this respect. The adrenal glands deserve further study in their relation to the formation of immune bodies.

DR. P. R. MEYER, Port Arthur, Texas: Dr. Parmelee, you mention the routine use of sulfathiazole in your cases. Do you prefer it to other sulfonamide compounds?

DR. A. H. PARMELEE, Oak Park, Ill.: Yes, partly because of convenience, as we had the sulfathiazole available in powder form. Sulfathiazole was used because colon bacillus and staphylococcic infections predominated. Infants do not tolerate sulfanilamide as well as sulfathiazole.

DR. H. A. TREMAINE, Boise, Idaho: In my part of the country it may be from two to twenty-four hours before a newborn infant is examined. During this period, in which neglect is so obvious, I have seen robust infants with body temperatures below 96 F.; these infants can be damaged by such chilling. Why cannot all newborn infants be considered as in potential danger and be better cared for prior to pediatric examination?

DR. A. H. PARMELEE, Oak Park, Ill.: The immediate care of the newborn infant would, of course, depend on local conditions; however, our obstetric colleagues are becoming more and more cooperative and more and more pediatric minded. When obstetricians and pediatricians work together, neonatal mortality is reduced. Progress in regard to mortality during the first twenty-four hours remains at the same level. A hospital in New Orleans has organized a good neonatal team, composed of an obstetric resident, a pediatric resident, a delivery room nurse and a maternity nursery nurse. This foursome rotates in order, so that at least three members are experienced in observing danger signals in the newborn infant. In this way, neonatal mortality can be reduced, as it is necessary to train each attendant adequately, and in the simple routines, too. I can frequently tell when a new obstetric resident comes on the service by the abrasions within the infants' mouths from manipulations with a gauzed-covered finger. Such abrasions can be a source of infection.

DR. M. C. CARLISLE, Waco, Texas: What are your criteria for discontinuing therapy in cases of osteomyelitis in the newborn? How long do you continue sulfonamide or penicillin therapy?

DR. A. H. PARMELEE, Oak Park, Ill.: My experience is limited. Such criteria would be based entirely on clinical manifestations. One infant is still getting penicillin after seven weeks; administration of the sulfathiazole, however, was stopped.

DR. C. H. FARMER, Macon, Ga.: What about penicillin therapy for tetanus neonatorum? I indirectly advised the therapy in 2 cases of suspected tetanus, and the infants recovered after treatment with the drug. In a third case, in which a culture yielding the tetanus bacillus was obtained from the cord, the infant did not survive.

DR. A. H. PARMELEE, Oak Park, Ill.: Dr. Farmer's observation is interesting inasmuch as I did not consider tetanus a problem any more. The older textbooks used to devote a great deal of space to this condition. I have never seen a case.

DR. E. H. WATSON, Ann Arbor, Mich.: Is it not a fact that the leukocyte count in infants with sepsis may be rather high?

DR. A. H. PARMELEE, Oak Park, Ill.: The leukocyte count is almost uniformly high, particularly the percentage of polymorphonuclear cells.

DR. R. M. KEMPTON, Saginaw, Mich.: Would it be worth while in the case of aseptic fat necrosis in infants to give prophylactic chemotherapy?

DR. A. H. PARMELEE, Oak Park, Ill.: I do not think so, for aseptic fat necrosis is a relatively common occurrence in the newborn.

DR. H. T. KNOBLOCH, Bay City, Mich.: Does fat necrosis result from hypodermic therapy?

DR. A. H. PARMELEE, Oak Park, Ill.: In my opinion, hypodermic medication should be kept at a minimum to avoid the tendency to fat necrosis in the tender skins of newborn babies.

DR. B. M. KAGAN, Chicago: What effect do the sulfonamide drugs have on the kidneys of the newborn?

DR. A. H. PARMELEE, Oak Park, Ill.: That aspect was discussed at a round table discussion yesterday. There is no evidence that the kidneys of the newborn are endangered by therapeutic doses of the sulfonamide drugs. It is astonishing what large doses of the drugs are well tolerated by the kidneys of the newborn.

DR. E. H. WATSON, Ann Arbor, Mich.: A baby admitted to my service had been perfectly well until the eighth day. The mother had a mild infection, which was indicated by a change in character of the lochia. My associates and I asked ourselves then whether we should formulate a rule that the baby be taken off the breast when the mother has any mild infection. Do you have an opinion in this regard?

DR. A. H. PARMELEE, Oak Park, Ill.: I am glad that Dr. Watson brought up that question. At Cook County Hospital there is an isolation ward where mothers with infections or elevated temperatures are placed. Their babies are taken off the breast. The health of the mother may have more to do with the condition of the baby than has hitherto been recognized. For example, when I first came to Cook County Hospital, I was surprised to observe that babies were born with a congenital pyoderma. It must be assumed that for bacteria to get across the placenta it must become infected. Dr. A. Levinson, of Chicago, reported a Salmonella infection of the meninges of a newborn infant whose mother had a diarrhea, the mother's stools when cultured yielded the organism.

DR. R. M. KEMPTON, Saginaw, Mich.: In the busy nursery the routine is to feed many premature infants by gavage. Should such babies be given sulfonamide drugs prophylactically?

DR. A. H. PARMELEE, Oak Park, Ill.: I am of the opinion that gavage is a delicate procedure. It must be done correctly. One nurse cannot do it alone. There is no trauma to the esophagus; the danger is from aspiration.

DR. D. J. BARNES, Detroit: On the other hand, feeding the baby by bottle may prove as hazardous as a gavage feeding if the baby is premature, weak and unable to draw on the nipple properly. In such instances gavage may be the safer procedure.

DR. R. D. COX, Worcester, Mass.: Since the umbilicus is a common portal of entry of infection, there must be some relation between the kind of care given the skin and the tendency to sepsis.

DR. A. H. PARMELEE, Oak Park, Ill.: I have no experience in this respect. At Presbyterian Hospital in Chicago my associates and I treat all babies "dirty." Except for using oil around the buttocks, we leave the skin alone. In spite of this, we have had several cases of sepsis. Treating the skin by "intelligent neglect" reduces greatly the number of cutaneous infections. We now service each baby in his crib. This minimal amount of handling is important in reduction of infections of the skin in newborn babies. Earlier in the discussion, my attention was called to tetanus of the newborn. I have never seen a case. I have seen 1 case of diphtheria of the umbilicus in a newborn.

Of course, the umbilicus of the newborn must be dressed carefully and physicians must be cautioned about the ease with which umbilical infections may occur as a result of careless technic.

DR. E. H. WATSON, Ann Arbor, Mich.: What do you think of the routine use of ammoniated mercury ointment in the prevention of cutaneous infection in the newborn?

DR. A. H. PARMELEE, Oak Park, Ill.: My opinion is that this procedure is too drastic and does not yield any better protection than the more conservative methods of caring for the skin of the newborn.

DR. J. B. STONE, Richmond, Va.: Why cannot the same thing be said about the application of oil to the skin?

DR. A. H. PARMELEE, Oak Park, Ill.: That point is well taken; of course, oil is not so dangerous as ammoniated mercury ointment may be.

DR. H. T. KNOBLOCH, Bay City, Mich.: In my opinion, there is a tendency also for the skin to be irritated by chemicals left in clothing by laundries.

DR. A. H. PARMELEE, Oak Park, Ill.: This is true. Now, since we have the babies' clothes washed separately, and by special processes, we find them less irritating to the babies' skin.

DR. D. J. BARNES, Detroit: I wonder whether the use of commercial diaper services is a safe procedure for nurseries.

DR. J. L. REICHERT, Chicago: There is no doubt that the diapers supplied by such services are sterile for the usual pyogenic organisms, but there is no getting rid of the spore forms which cause diaper difficulties in the older infant. For the newborn, because ammoniacal diaper difficulties are not encountered, the commercially laundered diaper is satisfactory.

DR. W. E. WHEELER, Columbus, Ohio: Is sepsis of the newborn a new problem? Is it caused by too much handling of the newborn infant?

DR. A. H. PARMELEE, Oak Park, Ill.: I believe that since nurseries for the newborn are now in the hands of pediatricians there is more handling of newborn infants. Therefore, standards must be established and rules set down which all physicians will obey for the safety of the babies. There must be a standardized technic to follow. A strong hospital committee is necessary to establish the regulations. In Chicago, there is a strong department of health which cracks down on

the offenders of good technic. A good nursery supervisor with complete control is also necessary. A constant personnel is needed. The personnel must stay long enough to become adequately trained. For example, in a small hospital in which the maternity nursery census is about 10, the relief nurse who knows nothing of nursery technic may be a source of trouble. The residents and interns must be well informed in technic and well trained.

I went to a hospital in which there were about twenty physicians caring for infants in the nursery; each physician handled his baby in his own way. This situation was an impossible one. There must be standardization, so that the supervisor and her nurses may learn and carry out a good technic, as recommended by the hospital committee.

DR. E. B. SCHUSTER, Pittsburgh: Have you any experience with sterilizing a room with ultraviolet light or aerosol spray? Do you have experience as to what happens when a baby is kept with the mother in her own hospital room?

DR. A. H. PARMELEE, Oak Park, Ill.: I have no experience from which I can answer either of these questions. Dr. Iwan Rosenstern, at the Cradle, Evanston, Ill., probably can give you information on the use of ultraviolet light in the prevention of infections in nurseries. As for keeping the baby in the room with the mother, I am much interested in this problem. However, I think it opens up new avenues of infection. The idea is not altogether new, but it will be a revolutionary step. A good many difficulties in the technic of asepsis arise with this arrangement.

DR. J. L. REICHERT, Chicago: At Nassau, where there is only a two hundred and seventy bed hospital for the city, this arrangement was considered ideal. The obstetric supervisor said it all but eliminated infections in the nursery and greatly increased breast feeding.

DR. C. C. FISCHER, Cynwyd, Pa.: What do you think of the routine use of vitamin K hypodermically? What about the routine use of masks?

DR. A. H. PARMELEE, Oak Park, Ill.: I am on the medical advisory board of the maternal welfare committee for Dr. H. N. Bundesen, the commissioner of health in Chicago; so I have some knowledge about the value of masks. At Michael Reese Hospital an experiment in which masks were discarded did not show that their removal was hazardous to the infants in the nursery. The kind of masks and the length of time they are used are important. At Cook County Hospital, masks are used as a matter of tradition, except in warmest weather when the humidity is high. I am lukewarm about the use of masks, especially if members of the personnel are impressed with the dangers of working in the nursery if they are not well. "If you have a cold, stay out of the nursery." Culturing of secretions from the noses and throats of the personnel is apt to create confusion and should not be done. Clinical evidence of illness in the personnel should be the basis of exclusion from the nurseries.

As for the routine use of hypodermic therapy, I repeat that it should be kept at a minimum.

DR. W. E. WHEELER, Columbus, Ohio: Do you believe that a baby has more immunity for strains of bacteria derived from his mother than for those from other sources?

DR. A. H. PARMELEE, Oak Park, Ill.: There is reason to believe that babies do get some antibodies from their mothers. That is why calves have immunity to colon bacilli derived from the udder of their mothers. The age of the baby is important, too. Infants under 6 months of age do not produce antibodies against an antigen as readily as do older infants.

DR. W. E. WHEELER, Columbus, Ohio: In the future in planning a hospital, instead of allowing for a large nursery, should one give thought to the building of smaller nurseries, even at additional expense?

DR. A. H. PARMELEE, Oak Park, Ill.: Thought has been given to this plan. It can be done by building smaller nursery units. A big nursery, however, may be divided into units, so that one nurse will be responsible for only 8, or at most 12, babies. The Children's Bureau has a booklet on standards for nurseries, and hospital architects are generally aware of the problems. A nursery should always be on the same floor as the mothers are, and both the nursery and the obstetric floor should be under central single supervision.

DR. E. B. SCHUSTER, Pittsburgh: Where do you draw the line at which you take a baby off breast feeding? What about the removal of an infant from the breast if the mother has a cold?

DR. A. H. PARMELEE, Oak Park, Ill.: If a mother is febrile, with a temperature of 100.4 F. or more, the baby is taken off the breast; but we have not removed a baby from the breast because of the common cold.

DR. H. T. KNOBLOCH, Bay City, Mich.: What do you think of stimulating antigermicidal activity in the baby by giving the mother small shots of antigen preparations?

DR. A. H. PARMELEE, Oak Park, Ill.: This procedure must wait until more is known of how antigens act on the baby. It is known that antibodies get to the baby in diphtheria or whooping cough from the mother, but what happens in an invasion of pyogenic organisms is not known.

II. Surgical Procedures in Pediatrics

Dr. Edward J. Donovan, who was to have led the discussion, was called back to New York. Dr. Robert E. Gross, of Boston, spoke on the topics which follow, illustrating each with many lantern slides made from drawings and photographs.

Compression of the Trachea and Esophagus.—Patients with this anomaly have difficulty in breathing and swallowing. The breathing is noisy and often is obstructed during both inspiration and expiration. Laryngotracheal infection is frequent and severe. If the compression is not relieved, death frequently occurs before the end of the first year of life. These children often lie constantly with the head retracted, which is indicative of pressure from without the trachea rather than of pressure from an intrinsic obstructive lesion.

The diagnosis can oftenest be made by means of the roentgenogram. Barium sulfate may be used in the esophagus, but only iodized oil should be used in the trachea. The anteroposterior view may be of little or no value, but the compression defect may be plainly seen in the lateral view.

This compression of the trachea and/or the esophagus is caused by an abnormal relation of the great vessels to these organs. The trachea and the esophagus may pass through a double aortic arch, with insufficient space between its limbs to allow their unobstructed passage. Compression can also be caused by the right subclavian artery arising directly from the aortic arch and passing to the right behind the esophagus on its way out of the chest. The innominate artery may also arise in such a manner that it presses on the trachea.

By means of a left transpleural approach, Dr. Gross made exploration in 6 cases in which he observed a double aortic arch or an abnormal subclavian artery.

Atresia of the Esophagus.—Babies with this anomaly are generally born with a gap in the esophagus, the upper part ending as a blind pouch and the upper end of the lower part opening into the trachea just above its bifurcation. Three other modifications of this relationship have been classified by Ladd and associates, but the particular type described makes up more than 90 per cent of the total number of cases reported.

The diagnosis can be established if an obstruction is met in attempting to pass a catheter into the stomach and its presence is then confirmed by passing a small amount of iodized poppyseed oil through the catheter and getting a roentgenogram. This roentgenogram should include the abdominal cavity, since the opening from the trachea into the lower part of the esophagus will cause the stomach and intestine to be entirely filled with air.

A catheter should be passed through the baby's nose to the bottom of the blind upper esophageal pouch and left strapped in place. Continuous suction should be maintained through the catheter in order to prevent any secretion from spilling over from the esophageal pouch into the trachea.

Formerly these babies were treated by the performance of a three stage operation, consisting of (1) separation of the lower part of the esophagus from the trachea with closure of the lower end of the esophagus and of the opening into the trachea and the formation of a gastrostomy opening for feeding purposes; (2) removal of the blind upper pouch of the esophagus from the mediastinum in order to place it subcutaneously on the anterior thoracic wall and (3) formation of a tube from skin flaps connecting the lower end of the esophagus to the gastrostomy opening in the stomach. This method of treatment has proved to be generally unsatisfactory, not only because it required years for its completion, but, especially, because the gastrostomy opening is a fistulous tract without epithelial or mucous lining, and so tends to contract as time goes on. Instead of the tube formed from skin, a loop of ileum has been brought up to serve as a passage between the transplanted esophagus and the stomach.

Dr. Gross reported that he has abandoned this multiple stage operation entirely in favor of a one stage operation by means of which, by right retrophleural approach, the lower portion of the esophagus is detached from the trachea and the opening into the latter is closed. The upper esophageal pouch is then freed as far up as possible in order to gain length, and the ends of the esophagus are brought together in an end to end anastomosis. A gastrostomy is then performed and the baby is fed for ten days or two weeks through the opening, before it is allowed to close.

Dr. Gross emphasized that babies with this anomaly should be prepared for operation as soon after birth as possible. The preparation should consist of (1) keeping the upper esophageal pouch clear of excess secretion by suction applied to the indwelling catheter; (2) use of penicillin and sulfadiazine to prevent or to combat any pneumonic process in the lungs; (3) administration of blood through a blunt needle tied into a vein in the ankle during the operation, (4) administration, as needed, of isotonic solution of sodium chloride intravenously and by hypodermoclysis, with care that an excess which will produce edema is not given. Dr. Gross reported that his colleague, Dr. Orvar Swenson, Boston, has had only 1 death in his last 15 consecutive cases of atresia of the esophagus.

Imperforate Anus.—There are four types of imperforate anus. The commonest type is one in which the rectal pouch comes down close to the perineal floor with no fistulous openings. In this type the anal sphincter is usually present and the closed anus is visible as a dimple-like depression. In the second type the blind

rectal pouch opens by a fistulous tract into the urethra, or into the vagina if the patient is a girl. The third type presents a fistulous opening into the perineum anterior to the anal opening. In the fourth type the anus is normal, but at a short distance above it the rectal canal narrows, even to the extent of becoming a fibrous cord for varying distances.

In cases of the first type, a roentgenogram should be made as soon as the baby has swallowed sufficient air (about twelve hours after birth), with a lead marker on the anal dimple, and with the child held vertically with the head down. This position allows the air to outline the rectal pouch, so that the distance between it and the skin is indicated. If this distance is not too great, an operation should be performed to bring the rectal pouch down and suture its edges to the skin. Dr. Gross emphatically warned against the method which has often been used to correct this defect in babies, by that of plunging a knife through the anal dimple in an attempt to open the blind anal pouch.

If the rectal pouch can be brought down, control of the anal sphincter will develop in about 80 per cent of cases and will fail only in those children who have an additional congenital defect in neuromuscular development. At times the surgeon may be forewarned of a lack of normal neuromuscular development by an unusual flabbiness of the perineal structures. When the rectal pouch is too high to be freed and brought down, or when fistulous openings must be repaired, a high sigmoid colostomy should be done. At a later age (2 to 3 years) the indicated additional surgical measure may be carried out. For example, a combined abdominal-perineal operation may be done, in which the abdomen is opened with section of the floor of the peritoneum. The rectal pouch is then freed until it can be reached from below and sutured to the skin in the manner mentioned previously.

If the existing fistulous opening is sufficiently large to allow the mother to keep the rectum free from inspissated fecal material by daily irrigation through a catheter inserted into the fistula, all surgical intervention may wait until growth makes the surgeon's task somewhat easier. Only when the fistula present is at a low level and the rectal pouch is readily accessible is early repair advisable. The colostomy should not be done at too low a level, since it may interfere with bringing the rectal pouch down when the later operation is attempted.

Sacral Teratoma.—Sacral teratoma is present at birth as a round, smooth tumor, often as large as the child's head, attached to the dorsum of the sacrum. This tumor is usually of mixed tissue type and frequently is both in front of an behind the sacrum. When the tumor is completely removed during early infancy, the prognosis is good, but delay into later childhood makes the outlook progressively worse. Despite the wide area that must be dissected, the function of the anus and rectum is seldom disturbed. The best incision is a transverse one.

Congenital Diaphragmatic Hernia.—Congenital diaphragmatic hernia should be operated on soon after birth, while the infant is in good condition. Intratracheal anesthesia should not be attempted. No barium sulfate should be given. The distribution of air shown in a roentgenogram will establish the diagnosis.

The approach should be made through an incision into the abdominal wall, in preference to one through the thoracic wall. When the thoracic route is used, it is often difficult, or impossible, to replace the viscera into the small space afforded by the abdominal cavity. With the abdomen open, the viscera can be brought down readily and the defect in the diaphragm closed. When the abdominal incision is closed, if the tension is too great only the peritoneum and skin need be brought together, and the intermediate layers may be sutured together at a later operation.

The edges of the diaphragmatic defect need not be scarified but should be overlapped with interrupted mattress sutures of silk. An important step in the operation is the thorough removal of air from the pleural cavity when the operation is completed. This is done by leaving a catheter in the thoracic cavity, withdrawing the air through it and then removing the catheter, after which the remainder of the opening is carefully sutured.

Coarctation of the Aorta.—Dr. Gross gave credit to Dr. John P. Hubbard, of Boston, for suggesting the possibility of surgical relief for this condition. The infantile type of coarctation, which is characterized by a wide area of narrowing (atresia) commonly associated with other cardiac anomalies, cannot be treated successfully. Patients with this defect usually die in the first or second year of life.

Children with coarctation may be divided naturally into four approximately equal groups on the basis of prognosis: 1. About 25 per cent of these patients have a reasonably long and comfortable life expectancy. 2. About 25 per cent contract a superimposed infection, and of these, even with modern chemotherapy, approximately one fourth (25 per cent) die. 3. Another 25 per cent die of rupture of the aorta. Usually the rupture is preceded by hypertension, but it may occur in the presence of normal blood pressure. About 25 per cent of ruptures of the aorta take place in patients in the third decade of life. 4. Cardiac failure, in the natural course of the condition, accounts for the death of the remaining one fourth of these patients. About 40 per cent of patients with coarctation die between 15 and 30 years of age.

A diagnosis of coarctation of the aorta may be established by the following criteria: 1. The blood pressure in the arms is higher than in the legs. 2. In older children there is an increased collateral circulation in the intercostal arteries. Usually by the eighth or ninth year of life the enlarged intercostal arteries have increased the size of the indentation through which they pass beneath the ribs so that it is detectable roentgenographically. 3. Heart murmurs are variable. Most patients have a systolic murmur; others have only a systolic swish, heard best at the back. Some patients have no murmur, and others may have a continuous murmur. 4. The electrocardiogram usually shows only myocardial degeneration.

Resection of a portion of the aorta with an end to end anastomosis was done on 40 dogs before it was attempted on a child. This operation has not been performed on a child younger than 6 years of age. The principal contraindication is arteriosclerosis at the site of coarctation. While arteriosclerotic changes may occur early in life, they need not prevent successful surgical repair in some patients up to the seventeenth, or even the twentieth, year.

Dr. Mannerheim, of Stockholm, Sweden, suggested that lack of detectable pulsation in the femoral arteries may assist in establishing the diagnosis even in very young children.

Omphalocele (Umbilical Hernia).—The treatment for omphalocele is surgical closure of the defect in the abdominal wall as soon after birth as possible. Dr. Gross expressed the opinion that some of his earlier failures may have been due to the great increase in intra-abdominal pressure caused by replacing the viscera within an underdeveloped abdominal cavity and closure of all the layers of the abdominal wall over them. The relative size of the abdominal cavity and the defect in the abdominal wall would, therefore, have an important bearing on the possibility of complete repair with survival of the infant. To meet this difficulty, Dr. Gross has made two successive modifications of the earlier operative method. First, after resection of the peritoneal sac and closing of the peritoneum, only the skin was brought together and the closure of the remaining layers of the abdominal wall

left for a second, elective, operation. Recently, the procedure has been further simplified by thoroughly cleaning the peritoneal sac, then painting it with iodine and covering it only with skin, which is freed by thorough, wide dissection to such an extent that its edges can be brought together without tension. This method has proved very satisfactory and has been successful when the defect has been very large, even in those cases in which a large portion of the liver was visible in the defect and the prognosis was formerly regarded as hopeless.

Undescended Testis.—Dr. Gross asked the secretary, Dr. Lewis K. Sweet, to present the subject of undescended testis.

Diagnosis.—If the scrotum of the young child presents a normally wrinkled appearance, it is not probable that he has an undescended testis. If the testis is in the inguinal canal or within the abdomen, the scrotum is smooth and usually small. If the scrotum is normally wrinkled, the testis will be found below the inguinal canal or within the scrotum some time during the first few months of life.

When the examiner finds the testis within the inguinal canal and presses with his fingers in an attempt to move the testis toward or into the scrotum, the following observation is important: If the testis can be moved some distance toward the scrotum, with its long axis remaining parallel with that of the canal, it will probably complete its descent naturally. In the presence of a well developed, wrinkled scrotum, descent will almost certainly occur. If, however, pressure from above on the testis causes it to move only a short distance, while it turns to a position approximately at right angles to the canal, it is evident that the gubernaculum is attached at a high level and natural descent is impossible. If, in addition, the scrotum is smooth, surgical treatment is clearly needed.

Medical Treatment.—Dr. Gross has not observed any benefit from the injection of any gonadotropic substance. He is of the opinion that most, if not all, of the results recorded as successful which were credited to this method of treatment have been obtained in children who did not have an undescended testis or in those in whom the testis would have descended later, without treatment. If injection of gonadotropic substances is thought worthy of a trial, no such treatment should be begun before the age of 7 years. When such injections are given during infancy, abnormal enlargement of the penis is the only measurable result.

Surgical Treatment.—If the testis cannot be palpated, it may be within the abdominal cavity or it may be congenitally absent. The latter possibility should be clearly called to the attention of the parents before operation.

The inguinal canal should be opened widely to permit a good exposure of the internal ring. Dissection should then be started as high up on the cord as possible and carried on throughout the operation from above downward. When all dissection, both without and within the cord, is only in this direction, no vessels are injured and little or no bleeding is encountered.

After all the steps enumerated by Ladd and Gross (Abdominal Surgery of Infancy and Childhood, Philadelphia, W. B. Saunders Company, 1941, pp. 376-377) have been carried out, there may still be insufficient gain in the length of the cord to place the testis easily in the scrotum. It will then be necessary to gain the needed length by careful, painstaking division of the fibrous bands within the cord. While an assistant makes gentle downward traction on the cord, with the testis enclosed in a warm moist sponge, the operator should carefully divide each band that is under tension. (Incidentally, some bands must be divided at two or more levels if either remaining portion prevents full extension of the cord.) This method must often be continued until nothing remains of the cord except the vessels and

the vas deferens. These structures can be left with impunity without the support of fibrous tissue provided they have not been injured in any way.

When the cord is long enough so that the testis can easily be placed in the scrotum, the testis is carried into place by a suture passed through the root of the gubernaculum and from within out through the lower pole of the scrotum. The neck of the scrotum is then closed by a purse-string suture placed in front of the cord so that only the very tip of the little finger can enter beside the cord. The wound is then closed in layers, and the suture which has been used to carry the testis into the scrotum is removed.

No traction of any kind is attached to the testis. When the cord is sufficiently lengthened, traction is of no value and, even though very gentle, may be harmful. Since it is often necessary to free the vessels within the cord of all support, any pull on them would decrease their diameters, thus measurably decreasing the blood supply to the testis during the immediately critical postoperative period of recovery. Even the very gentle traction of a rubber band, advocated by Ladd and Gross, is thought to be inadvisable, and the Torek method of fastening the testis to the thigh should be abandoned.

During the past twenty or more years, Dr. Sweet has not used traction on the testis after an operation and only twice has the testis retracted from a satisfactory position in the scrotum. One of these retractions occurred in an infant 18 months old who was operated on for the relief of an incarcerated hernia and whose undescended testis was then placed in the scrotum. Afterward, it seemed probable that this failure was due to a false canal being made into the scrotum by the operator's finger being passed downward in a plane parallel with the true canal. The other retraction was in an older boy and occurred soon after the original operation. This may have been due to improper placing, or failure, of the purse-string suture at the neck of the scrotum.

No case has been encountered in which the testis could not be brought into the scrotum during a single operation. None of the vessels in the cord has ever been divided.

Time of choice for operation has generally been between 9 and 11 years of age. Other surgeons prefer to wait until the patient is nearer puberty. The earlier age has been chosen because it is thought that with the criteria mentioned earlier the necessity for operation can be determined with reasonable accuracy. Further, it is reasonable to suppose that when puberty ushers in its final rapid growth and development, it would be better to have the testis in its normal environment, without its having to undergo the disturbance of surgical intervention.

III. Mental Health: Emotional Status in the Newborn

The Emotional Status at Birth. Dr. Harry Bakwin, New York.

Many things have been taken for granted in the care of the newborn. There is good reason to believe that some present day methods need to be changed; others require further study. This paper is designed to be provocative rather than informative. It is my intention to raise some questions rather than to answer them.

The newborn is equipped with a well developed set of emotional responses. Observation of the prematurely born infant indicates that emotional reactivity is present several months before birth. Does the fetus exercise his emotions; or does emotional reactivity, like the respiratory mechanism, remain dormant until the moment of birth? If the fetus reacts emotionally, to what stimuli does he respond? There is much speculation on this subject, but reliable data are few. Dr. Lester

W. Sontag and his co-workers at Yellow Springs, Ohio, observed the movements of the fetus in various circumstances. The fetal movements may be divided into three groups: slow, squirming movements; sharp, kicking movements, and small rhythmic movements, referred to as fetal hiccups. The fetuses of mothers undergoing severe emotional stress exhibit many times the amount of activity which they previously exhibited. This observation was originally made by Whitehead in 1867.

When vibratory stimulation is applied to the mother's abdomen, the fetus responds with a typical Moro, or startle, reflex, convulsive movements of the extremities and an increase in the heart rate. The response to stimulation increases month by month and is greatest during the last few weeks before birth. In 1 fetus who was stimulated in this manner daily the response declined, instead of increasing as term approached. Not only did the response become less intense, but the duration was shorter.

According to Dr. Sontag, the infants of mothers who had undergone severe emotional stress late in pregnancy remained unstable and hyperactive for weeks, and in some instances for months. They cried a great deal and slept poorly. Most of them were difficult to feed; they had loose stools and gained weight poorly.

A further observation by Dr. Sontag was that the weight at birth in relation to height is less, on the average, in the more active fetuses than in those who are less active.

There is speculation on the meaning of the birth experience to the child and its relation to anxiety; but here reliable observations are lacking. In this connection it is reasonable to ask what effect, if any, anesthesia during labor has on the mother-child relationship. One young mother who had had only a small amount of nitrous oxide during labor said that having the baby had given her a sense of satisfaction which she would have had missed had she received deep anesthesia.

The emotional responses of the newborn may be divided into two groups: those which are pleasant, sometimes called positive responses, and those which are unpleasant, or negative, responses. Pleasurable responses are elicited by patting, rocking, warmth, snugholding and allowing the baby to suck. Displeasure is elicited by abruptly changing the infant's position, by sudden loud sounds, by hampering the infant's movements in an uncomfortable position, by a cold object applied to the skin, by a wet diaper and by hunger. The infant responds to disagreeable stimuli by crying. It is his way of expressing unhappiness.

The ability to respond emotionally is present in the newborn as part of the developmental process. It is not something which is learned. A basic principle of a child's development is that the maturing emotions require gratification if optimum health is to be attained. It follows that infants should be cuddled, patted and rocked. This concept represents a complete change from the teachings of the recent past. It is of some interest that the methods of eliciting pleasurable responses in babies, as worked out in the laboratory by careful observation, have been used intuitively by mothers through the ages.

The Obstetric Hospital.—The unphysiologic separation of mother and baby which is current practice in obstetric hospitals should be corrected. Indeed, steps have already been taken in this direction. The new George Washington University Hospital is setting aside a certain number of rooms where mother and baby can be near one another.

Another change needed in the care of the newborn relates to feeding. During prenatal life the fetus obtains his food in a continuous stream by way of the umbilical vein. A hunger rhythm does not develop until several weeks after birth. Consequently, the feeding demands of the newborn are irregular, both as to the

interval between feedings and the amount required at a feeding. Nurses can hardly be expected to bring the baby to his mother whenever he seems hungry. The only way that the natural feeding demands can be satisfied is by having the baby near his mother.

Fortunately, a rhythm of hunger develops at the age of 2 or 3 weeks. Thereafter, the large majority of infants will readily adjust to a four hour feeding schedule. A self-demand feeding schedule is then no longer necessary—nor is it desirable.

The practice of giving water and sugar solutions to newborn infants has been questioned, since breast feeding is apt to be less successful after the administration of a bottle. This custom was generally adopted about twenty-five years ago, after the discovery that what had previously been referred to as "inanition fever" was actually dehydration fever. The administration of water and sugar solutions by mouth has greatly reduced the incidence of dehydration fever; but dehydration fever is not known to interfere with general health.

A further advantage of discontinuing the routine administration of water to newborn infants is that it would eliminate one source of contagion in the nursery. (Routine weighings and taking of temperatures could also be eliminated advantageously, for the same reason.)

I am opposed to the routine bottle feeding of babies during the first three days of life, even though the mother is not going to breast feed her infant. Too little is known about the complex adjustments the infant must make at this critical period to interfere with physiologic starvation. There is reason to believe that early artificial feeding is one of the etiologic factors in tetany of the newborn.

There is general agreement among pediatricians that breast feeding is desirable and should be encouraged. The reasons have been stated frequently and need not be repeated here. I shall mention only one point, which in my opinion has not been sufficiently emphasized, that is, the ease with which the breast-fed infant regulates his food intake, in contrast to the difficulty which many artificially fed infants experience. The breast-fed infant takes from the breast as much as he wants or can get. If he has taken too much, he regurgitates the excess. It is an old observation that the amount of milk obtained may vary widely from one feeding to the next. Diarrhea in a breast-fed infant because of overfeeding is rare, and ordinarily not serious when it does occur.

With artificial feeding the situation is different. The cautious pediatrician will hesitate to give the large amounts of food which many infants require; hence, the child will cry because of hunger. If, in response to the entreaties of the parents, the pediatrician does increase the food intake, abdominal discomfort, diarrhea and vomiting may occur. It is worth considering whether the amount of unhappiness, as indicated by crying, incident to the difficulty in regulating food intake during the first six to eight weeks of life has an influence on the emotional development of the child.

Another point to consider is the matter of clothing. Until about twenty-five years ago it was customary to wrap the newborn snugly in his blanket. Bundling the young infant is, I believe, general practice among primitive peoples. Presumably, loose clothing was substituted because it gave the baby more "freedom." Is it not just as reasonable to assume that snug clothing gives the baby some of the support which he had during prenatal life, and which he needs during the early weeks of postnatal life? Dr. A. L. Gesell has expressed the opinion that the premature infant craves the tactile and thermal snugness of clothes and that there are emotional satisfactions in close-fitting garments. May not some of the soothing

effect which the baby seems to experience when taken outdoors be due to the fact that he is bundled?

Sensations in the Newborn.—The sensations—sight, hearing, muscle balance, smell and taste sense, and tactile, thermal and visceral sensibility—are well developed in the newborn. Since visual and auditory sensations require a certain amount of experience in order to be meaningful, they are probably of little significance during the early weeks of life. It is, nevertheless, wise to expose the infant to the sight of colorful and moving objects and to household sounds, since they are probably stimulating and provide preparation for the future.

In contrast to sight and hearing senses, the other sensations do not necessarily require experience. There is reason to believe, from the soothing effect on the infant of rocking and swaying, on the one hand, and his disagreeable reaction to an abrupt change in position, on the other, that the muscle sense is highly significant for the newborn. The same is true regarding the sensation of touch. Here, too, the newborn appears to derive pleasure from one's stroking and patting his skin. Is it not possible that the quieting effect of keeping an infant outdoors may be due, in part, to the movement of air on the skin?

The Initial Interview.—The initial interview of the pediatrician with the mother of a newborn baby should be devoted principally to a discussion of psychologic principles as they relate to her baby. Many mothers, having had examinations, during pregnancy, of herself, her urine and her blood and having gone to a hospital for the birth of her baby, come to believe that pregnancy and delivery are pathologic processes. Moreover, many mothers have the notion that child rearing is an exact science. For these reasons, the first task of the pediatrician is to allay anxiety. Pregnancy, delivery and child rearing should be presented as natural functions of a woman. A mother should be urged to rely on her intuitive reactions in her behavior toward her baby.

The importance of breast feeding should be stressed. Since some mothers get a sense of inadequacy if they later find that they are unable to nurse, discussion on this subject should always be qualified by a statement such as, "If breast feeding is unsuccessful, we can resort to the bottle. The important thing is an honest attempt to nurse."

A mother should know that feeding schedules need not be too rigid. The times of feeding which are prescribed and the amounts to be given at each feeding can be varied to suit the demands of the child.

Suggestions for a "Rooming-In" Nursery. Dr. P. A. McLendon, Washington, D. C.

The function of a maternity service is twofold: first, to provide for safe delivery of the mother, and, second, to provide proper care for the infant. The care of the infant is concerned with two factors: (1) protection against infection, and (2) cultivation of a normal relationship with the mother.

While I consider prevention of infection of paramount importance, it is not the purpose with which this round table discussion is concerned. I do believe the nursery arrangement we propose will go far toward solving some of the problems of widespread epidemics among newborn infants.

Cultivation of a normal mother-infant relationship presumes (*a*) breast feeding; (*b*) observation by the mother of her newborn child's development; (*c*) partial care of her newborn infant commensurate with her physical ability; (*d*) the consequent accumulation of knowledge of her infant's behavior characteristics, par-

ticularly in connection with hunger, and (*e*) confidence in her ability to interpret behavior expressions and to handle them properly.

Present nursery regimens make no provisions for any one of these problems. Such regimens stipulate regular intervals of visits of infants to their mothers for stated minimal periods. There is no time allowed for casual acquaintance of the infant to the act of nursing. Preparation of the mother's breast is a hurried procedure. The infant may have been brought in when not hungry, or when exhausted from a period of crying because of hunger. Neither state is conducive to normal nursing behavior, and the mother becomes upset because of her failure. This failure in nursing is further aggravated later in the nursery by the giving of a "routine house formula"—thus dulling the infant's appetite for the subsequent attempt at nursing. A few days of this routine is enough to discourage the average mother and infant and results in the usual complaint that "I did not have enough milk to nurse but a few days."

This routine of short visits to the mother during the stay in the hospital also defeats the other four factors in a normal mother-infant relationship. The infant is either crying vigorously when brought in or, in most instances, extremely sleepy. He is whisked away in too short a time for the mother to note what is meant by "satiety." Interim observation for interpreting the infant's noises and movements is not possible—nor may she observe the period of gradual awakening due to hunger. She has no opportunity to change the uncomfortable wet diapers or to note the character of normal breast milk or formula stools.

These deficiencies can be corrected by a return to complete rooming-in units for the infant or to nurseries arranged in close proximity to the mothers' rooms. These features may be supplemented by a combined bassinet and cabinet so constructed that it can be attached to the mother's bed. The bassinet should be in a convenient position for the infant to be taken out and replaced at the wishes of the mother; it should also contain supplies for the mother's use in nursing or in changing diapers. With the infant at the bedside, the mother can note and learn to interpret the behavior actions in the infant which may mean hunger or discomfort. The irregularly appearing hunger rhythms can be satisfied when they occur. The element of limiting the nursing period to minutes will not enter into the physical or emotional satiety of the infant's nursing. I believe this "self demand" or "self-regulating" method of feeding will make for more contented infants and will be conducive to increasing the number of the infants who are breast fed. This opinion is shared by many obstetricians who have experimented with the "rooming-in" and "demand" methods in the neonatal period.

Such an arrangement of nurseries is now under construction at the George Washington University Hospital. Single mother-infant units, four crib and eight crib nurseries offer any variety of infant care a mother may prefer. It is obvious that some mothers will not want any part of such infant intimacy! These units are so distributed that no infant is farther than 40 feet from its mother. The four crib units are between two semiprivate rooms. Provision is made for the isolation of both infant and mother in close proximity so that breast feeding need not be interrupted.

The pediatrician, obstetrician and nurse must, of necessity, be in accord in the management of a maternity service so arranged. There are many problems to be solved in this departure from present day nursery arrangement and procedure. Cooperation in every department is essential to success. It is the opinion of many that in the prenatal, as well as in the neonatal, period, are laid down the essentials of normal behavior in the child by the attitudes of understanding in the parents.

DISCUSSION ON PAPERS BY DRS. BAKWIN AND McLENDON

DR. H. A. MURRAY, Newark, N. J.: How is the demand for nurses to be met?

DR. P. A. McLENDON, Washington, D. C.: With a host of nurses' aides, adequately trained and supervised. The success of the program depends principally on the nurses.

DR. GLADYS C. WINTER, Teaneck, N. J.: How would you handle emergencies?

DR. P. A. McLENDON, Washington, D. C.: If the condition demands it, we have isolation rooms for mother and baby.

DR. J. A. DI LEO, New York: Is the mother always the best person to have around the baby? I work at a foundling hospital, where the babies are entered from the age of 4 days. I find that unmarried mothers have many difficulties in the care of their babies. For instance, cases of vomiting can usually be controlled easily by employing an impersonal feeder. We have had no cases of pyloric stenosis in well over 1,000 babies. Do you believe there is any relation between behavior vomiting and the development of pyloric stenosis?

DR. HARRY BAKWIN, New York: No.

DR. J. M. BATY, Brookline, Mass.: One of the reasons that mothers nurse their babies—perhaps the most important—is the attitude of the obstetricians. One of our associates in obstetrics has 95 per cent of his babies on breast feeding. He starts conditioning the mother in favor of nursing from the first visit and continues throughout pregnancy. Dr. S. H. Clifford and I have convinced the nurses to use the self-demand nursing method in the Boston Lying-in Hospital.

DR. HARRY BAKWIN, New York: How does this work?

DR. J. M. BATY, Brookline, Mass.: On the second day babies are taken out to get acquainted with their mothers. On the third day the baby goes to the mother regularly. If the baby suckles well, there is no difficulty. If he does not, he is taken back to the nursery. Then when he awakens and cries he is taken back to nurse. Most of the babies suckle less than six times in twenty-four hours.

DR. HARRY BAKWIN, New York: What do you do in Minneapolis, Dr. Platou?

DR. E. S. PLATOU, Minneapolis: Very much as has been expressed here. My associates and I follow Dr. Sedgwick in breast feeding.

DR. J. MARGOLIS, Coatesville, Pa.: Do you believe that mothers are happy about nursing their babies?

DR. HARRY BAKWIN, New York: Most of them are. It gives them a sense of achievement and a satisfaction which women who feed their babies artificially do not get.

DR. J. M. BATY, Brookline, Mass.: Administration of fluid can be overdone in the case of newborn infants. In many nurseries for newborn infants it has become routine practice to give fluids during the first three days of life in an effort to prevent the loss of weight that normally occurs during this period. This is unnecessary, since the infant does not require fluids at this age, and it may be harmful. The administration of fluids at this time interferes with the establishment of breast feeding and may result in the development of edema.

DR. J. S. WALL, Washington, D. C.: Is not use of the standard hospital formula even more pernicious?

DR. P. A. McLENDON, Washington, D. C.: Nurses need reeducation with regard to the mother-baby relationship. When I first suggested that babies be put

into the room with the mothers, the nurses were shocked. This attitude has changed.

DR. J. S. WALL, Washington, D. C.: In some Navy hospitals, with the wards for the newborn under pediatric supervision, 66 per cent of babies were being nursed at 2 months of age.

DR. G. L. BROOKS, Lewiston, Maine: The argument of nursing for psychologic reasons is unanswerable. All the other arguments seem to have been met.

DR. HARRY BAKWIN, New York: Dr. Brooks's statement is not altogether true. We know that human milk and cow's milk are differently constituted; though babies seem to do equally well on either milk, there may be subtle differences which one does not recognize. There are two metabolic differences between babies fed on the two types of milk which are worthy of mention. The baby who receives cow's milk retains more calcium and phosphorus than does the baby on breast milk. It is not known whether this has any practical significance. It does mean, however, that babies fed on cow's milk are different from babies who suckle at the breast.

DR. J. J. SHIELDS, Philadelphia: Do not babies cry whether they are bottle or breast fed?

DR. HARRY BAKWIN, New York: Usually the breast-fed babies cry less.

DR. F. R. JANNEY, Wauwatosa, Wis.: How do you feel, Dr. Bakwin, about visiting at children's hospitals?

DR. HARRY BAKWIN, New York: We encourage visiting at Bellevue Hospital. We believe that the psychologic advantages to the babies are greater than the danger of infection.

DR. J. S. WALL, Washington, D. C.: How about the crisis brought about when a mother visits an older child and then leaves the hospital?

DR. HARRY BAKWIN, New York: The situation with the older child is different. My remark relates to infants under 2 years of age.

DR. R. KING, Savannah, Ga.: How can the crying of young babies be controlled?

DR. HARRY BAKWIN, New York: The crying of young babies is due generally to physical causes, such as too much or too little food, swallowed air or a wet diaper.

DR. G. W. ESTY, Westfield, N. J.: One way to prevent crying at night is to shift the baby's playtime to the afternoon.

DR. W. F. BURDICK, Washington, D. C.: There would be less crying if the mother had the opportunity to get acquainted with her baby in the hospital.

DR. T. P. SALTIEL, Chicago: I have observed that there is more crying in homes where there is "doubling up" of families.

DR. J. MARGOLIS, Coatesville, Pa.: Does allergy to foods ingested by the mother cause crying in the breast-fed infant?

DR. HARRY BAKWIN, New York: Probably not. Occasionally a breast-fed baby reacts unfavorably to foods in the maternal diet, but it is doubtful whether this reaction can be referred to as allergic.

DR. D. C. PEWTERBAUGH, Chambersburg, Pa.: Is the use of pacifiers permissible?

DR. HARRY BAKWIN, New York: Yes. All through life man seems to require oral satisfaction. The infant sucks his thumb or a pacifier; the child chews gum

or bites his finger nails; the adult smokes and munches. In my opinion, these activities have the same quality. The pacifier has an advantage over the thumb in that it can be removed toward the end of the first year, whereas many children continue to suck the thumb for years.

DR. E. R. KIMBALL, JR., Evanston, Ill.: How about a rocking apparatus for a baby, similar to that which Dr. Gesell advocates?

DR. DOROTHY V. WHIPPLE, Washington, D. C.: The cradle has a pacifying influence. One of my patients has rigged up a cradle, electrically controlled by a button at the side of the mother's bed.

DR. F. R. JANNEY, Wauwatosa, Wis.: No one said anything about phenobarbital or atropine. Is their use passé?

DR. HARRY BAKWIN, New York: No. Phenobarbital is very useful.

DR. T. M. LAMB, Brooklyn: How do we know that crying is harmful?

DR. HARRY BAKWIN, New York: Crying is an expression of discomfort and should not be allowed to go on for too long a time.

DR. J. L. SHORT, Durham, N. C.: I am pleased to be present at the round table this afternoon and to hear expressed such sensible, humane, understanding views on the care of the newborn. These views are diametrically opposed to the rigid schedules advocated at the round table this morning by Dr. Blatz.

DR. W. E. BLATZ, Toronto, Canada: I must rally to my defense here. I maintain that the newborn does not possess knowledge of his "self demands" in the first three weeks. I believe the pediatrician's judgment, based on his own experience, is better than the child's or the parents' or the nurse's interpretation of the child's demands. There are only six reasons that a child cries—hunger, thirst, bowel and bladder distention, sex, pain and extremes of temperature. How can the child know his needs? Is this matter to be decided by the child, the nurse, the parent or the doctor and baby? Is "self-demand" feeding really good for a child? Start discipline early.

DR. S. C. HENN, Chicago: I believe that the home should be adapted to suit the baby's needs during the first month of life. Later a switch can be effected by adapting the baby to the needs of the household.

DR. G. F. WEINFELD, Highland Park, Ill.: Is a baby able to deal with reality and practical demands? It is known that 50 per cent of crying is due to hunger. The parents become anxious to appease the baby. I don't believe that feeding the baby every time he cries predisposes him when older to eating "all day long." In the animal kingdom, the bitch yields her teats to the demands of her puppies at any time. By yielding to his early demands, one allows an unfrustrated and gratified baby to develop into a child with a well integrated personality. Such a child is apt to be well adjusted socially and mentally later in life. Early adaptations to reality help later adaptations.

DR. A. L. LEVY, Newark, N. J.: The mother's attitude to feeding determines her attitudes to the other functions of the baby. Mothers should be taught to be elastic and practical and to avoid extremes.

DR. P. A. MCLENDON, Washington, D. C.: Regarding self-demand feeding schedules, rigid adherence to rules and regulations has been largely discarded. A schedule is followed if it permits the baby to do as he pleases. The child should be educated in mental development rather than be trained. A baby must be able to respond according to timing and the maturation principle.

DR. W. E. BLATZ, Toronto, Canada: Do not force the child, but put the issue squarely up to him for his own decision.

DR. HARRY BAKWIN, New York: Few pediatricians advocate a purely self-demand feeding schedule after the neonatal period. The newborn will not adjust easily to a schedule.

DR. G. F. WEINFELD, Highland Park, Ill.: Why should a child feel differently about feeding than about bladder evacuation? He is not told when to wet.

DR. W. E. BLATZ, Toronto, Canada: A child learns gradually to make his own decisions as he grows older. After he finds out that wetting causes discomfort, he stops it. By the time he is 20 years of age he is able to make rational decisions. Behavior can be controlled only by a fixed schedule.

DR. P. A. MCLENDON, Washington, D. C.: But should one force him?

DR. G. W. ESTY, Westfield, N. J.: In New Jersey my colleagues and I advise parents when to feed the baby. We tell them not to use the bottle as a pacifier and to try to interpret the other needs of the baby from the cry. Also, we teach them not to adhere to a rigid schedule and not to let the baby exhaust himself in crying for food.

DR. A. L. LEVY, Newark, N. J.: Does Dr. Blatz mean that frustration in early life is helpful?

DR. W. E. BLATZ, Toronto, Canada: We are exaggerating a baby's emotions in early life. There are only two emotions—fear and anger. Every baby is frustrated in some way every day of its life. Let the child cry it out during the first six weeks of life and get it out of his system, and then he will capitulate readily. Coddling and handling are also important during the first two months of existence, so why not set aside a wakeful period, say from 4 to 6 p. m., for unrestricted gratification? Anger is a pleasurable emotion, for it is an approach response. Many hurts are pleasurable.

DR. RUTH M. BAKWIN, New York: A baby must have satisfaction in this early period of life, so that he will be able to cope with later frustrations. Show him his boundaries and make him secure. He must have dependent security.

DR. W. E. BLATZ, Toronto, Canada: But dependent security must be transformed to independent security. He must learn to accept responsibility, and this is difficult. How does one know that he needs or wants help early? Parents have other things to do besides taking care of babies.

DR. G. W. ESTY, Westfield, N. J.: Is it a question of whether it is the doctor's or the mother's job to see that the baby takes 4 ounces (120 cc.) of food or whether the baby himself should decide this issue? Should the baby decide his own elimination? Should the baby decide whether he should sleep? Should the mother decide the child's needs, or should she mold the environment to suit the child? Is it autocratic rule or democratic control?

DR. W. E. BLATZ, Toronto, Canada: I don't know what you mean by the terms "autocratic" and "democratic," but I know there are certain things one cannot do; that is, one cannot make the baby sleep, eat or eliminate, for that is the child's business. But shouldn't the parent accept the responsibility for nursing care?

DR. HARRY BAKWIN, New York: Are there any opinions on snug clothing versus loose clothing?

DR. J. L. SHORT, Durham, N. C.: Swaddling frequently causes miliaria.

DR. T. P. SALTIEL, Chicago: It was believed in bygone days that swaddling prevented deformity in rickets. Moreover, infants were so clothed to fit snugly in the slings carried by Indians.

DR. J. S. WALL, Washington, D. C.: The custom of swaddling babies is an ancient one. The change to looser clothing is a decided improvement. For the mother's information during pregnancy, I recommend that she read "The Dark River," in which pregnancy and birth took place without aid of the obstetrician.

DR. HARRY BAKWIN, New York: You feel that loose clothing is preferable?

DR. J. S. WALL, Washington, D. C.: Yes, because activity seems more physiologic. However, the only 2 children I know who were swaddled and tied to a board did very well and grew straight and strong.

DR. M. B. LOW, Greenfield, Mass.: May it not be that some babies need to be bound or clothed loosely, and others more tightly?

DR. HARRY BAKWIN, New York: The baby is snug in utero. Are there any opinions regarding the influence of anesthesia during delivery on the mother-child relationship?

DR. RUTH M. BAKWIN, New York: I believe that anesthesia is given oftener than mothers desire.

DR. T. M. LAMB, Brooklyn: In the Brooklyn Hospital mothers are willing to forego anesthesia in premature births.

DR. MARYELDA ROCKWELL, Clinton, Iowa: Many mothers complain that they don't know whether they have had a baby or not after delivery under anesthesia.

Book Reviews

Human Genetics. By Reginald Ruggles Gates. Volumes I and II. Price, $15. Pp. 1,425, with 326 figures. New York: The Macmillan Company, 1946.

Gates's "Heredity in Man," published in 1929, may be considered the forerunner of the present publication. However, the new work, "Human Genetics," includes so many additional chapters and improvements that it may be looked on as an entirely new attempt to compile the present day knowledge of human genetics. An introductory chapter on "General Principles of Heredity in Man" acquaints the reader with the terminology used by geneticists and with the principal laws of inheritance. Physicians who do not read genetic publications regularly will find in this chapter explanations for such terms as "penetrance," "normal overlaps," "expressivity," "pleiotropy," "anticipation," "homochronous heredity" and many others. Two additional chapters of a general character deal with human cytology and with linkage. The inheritance of some normal traits is discussed in four chapters, which deal with color of the eyes and of the hair, blood groups, stature and size and with such anthropologic characters as the shape of the head, color of the skin, shapes of hair and many others. The bulk of the book is concerned with abnormalities of the various organ systems. There is a thorough discussion of the hereditary variations and abnormalities of the eye. Paragraphs on epicanthus, strabismus, nystagmus, microphthalmos, megalocornea, aniridia, cataract, retinitis pigmentosa and optic atrophy contain much of interest to the pediatrician. One chapter is devoted to abnormalities of the ear and to hereditary deafness. Many diseases of the skin are notoriously heritable and a knowledge of the modes of inheritance of such disorders can be of definite practical value. Xeroderma pigmentosum, epidermolysis bullosa, Milroy's disease, keratosis follicularis and pilaris, the various forms of ichthyosis, psoriasis and many other abnormalities of the skin are briefly described and the facts concerning their heredity compiled. Abnormalities of the nails and teeth are included in the review. Two chapters deal with abnormalities of the limbs and other parts of the skeleton. They represent a careful collection of genetic data on many pediatric subjects. Among the heritable metabolic defects cystinuria, alkaptonuria, pentosuria, tyrosinosis, porphyria, hemochromatosis, glycogen disease, diabetes mellitus and diabetes insipidus are thoroughly discussed. The chapter on hemophilia and related hereditary conditions contains a wealth of information which indicates that some of the current views concerning hemophilia must be revised. Thus, the idea that male bleeders cannot transmit the disorder has been clearly disproved. There is ample evidence that females can be bleeders. The gene for hemophilia, which is usually sex linked, can occasionally be simple dominant or recessive. The genetic aspects of many other disorders of the blood are well covered. Elliptocytosis, sicklemia, thalassemia, acholuric jaundice, eosinophilia and many other abnormalities of the blood are considered from the genetic point of view. Two chapters deal with hereditary syndromes and congenital anomalies. Harelip and cleft palate are included among the abnormalities of the alimentary canal. The literature on this subject is well reviewed, and it is obvious that the mode of inheritance of these defects is still obscure. Quotations of families in which pyloric stenosis or appendicitis occur frequently are of great interest, but one must be cautious in attributing such a familial incidence to genetic factors. Two chapters of general biologic and medical interest deal with twins and

twinning and with sexual and intersexual conditions. The genetic aspects of muscular defects and of the abnormalities of the nervous system are thoroughly reviewed and many pediatric subjects are included in these sections. One chapter is devoted to the inheritance of mental defects and one chapter to the genetic aspects of cancer.

The book is written with great objectivity, and quotations of controversial material are included. In many instances the author criticizes the articles reviewed, and states his own opinion. Although genetic factors are stressed throughout the book, environmental factors are not minimized in the discussion of the etiology of diseases. The book contains thousands of references, complete even to the full title of the article cited, and an excellent index of 89 pages. These two volumes represent the modern standard work on human genetics, which should be included in every medical library.

Intracranial Complications of Ear, Nose and Throat Infections. By Hans Brunner, M.D., Associate Professor of Otolaryngology, University of Illinois College of Medicine, Chicago. Price, $6.75. Pp. 444, with 95 illustrations. Chicago: The Year Book Publishers, Inc., 1946.

This excellent monograph represents the first unified consideration of an important subject to appear in the English language. As such it warrants a position among the eminent contributions of Braun, Eagleton, Atkinson and others in its particular field.

The volume reflects the author's extensive studies and interest over a twenty-five year period and is particularly timely in its analysis of the role of chemotherapy in relation to otorhinogenic complications. No one will deny the introductory contention that diagnosis and treatment of these conditions are often more difficult than before the introduction of the newer agents. The advantages, uses and limitations of present day therapeutics are, for the most part, well presented.

Subject matter is divided into chapters on anatomy and physiology, inflammatory diseases of the dura mater, inflammatory diseases of the dural sinuses, leptomeningeal inflammation, brain abscess and encephalitis. Subheadings deal with pathology, symptomatology, prognosis and treatment in each considered topic. Outstanding among these is the presentation on pathology, with many fine diagrams and photomicrographs.

Exception might well be taken to dogmatic statements which appear with a certain regularity throughout the text. In a consideration of the operation on the lateral sinus the use of a gouge is advocated, whereas the majority of otologic surgeons today seem to feel that less hazard accompanies the use of tangential thinning of the bony wall by careful curettage until initial exposure is accomplished. (The author's detailed consideration of traumatic sinus thrombosis bears out well the dangers of accidental injury to the sinus wall.) In one section one reads that the masking effect of sulfonamide compounds is "important but apparently has been overemphasized," while in the next chapter one is told that "the sulfonamides may have a disastrous masking effect if the surgeon is not familiar with the pathology." Certainly one cannot allow to pass unchallenged a statement which reads: "If penicillin is prescribed, pyramidon (3-5 gms. daily) should be added, to constrict the blood vessels and reduce the exudation of serous fluid." Or this sentence: "It is fairly well established that there is a causal relationship between tonsillectomy and poliomyelitis, especially between recent tonsillectomy and bulbar poliomyelitis."

The text, on the whole, is fluid and readable. References at the end of each chapter, though not extensive, usually include the most important writings on the

subject. The index is excellent. There is no doubt but that Dr. Brunner's book merits wide acceptance and study by otolaryngologists, pathologists, neurologists. neurosurgeons and pediatricians.

Medicina infantil, pediatria y puericultura. Juan P. Garrahan, Director of Institute of Pediatrics of the Faculty of Medical Sciences of Buenos Aires. Sixth edition. Price, unknown. Pp. 1,076, with 16 plates and many illustrations. Buenos Aires: Editor "El Ateneo," 1946.

This comprehensive textbook of pediatrics, written originally in 1921, has been thoroughly revised in this sixth edition with new chapters added on Liver Diseases, Jaundice, Purpuras and Hemophilia, Hypertrophy of the Thymus and Stridors, Allergy, Neurology of the Child, Mental Hygiene, Psychiatry of the Child, Penicillin, Orientation Toward Glandular Therapy, Emergency Pediatrics and The Professional Behavior of the Pediatrician. In addition to these new chapters, the entire book has been brought up to date.

Dr. Garrahan's textbook, which can be said without exaggeration to occupy a position of preeminence in the eyes of Spanish-speaking physicians, is richly deserving of the highest approbation. The author's almost uncanny familiarity with the literature of the world together with his critical treatment of each subject in the light of extensive clinical experience makes this book invaluable to the practitioner of Spanish America.

In many respects, the book meets admirably the needs of his probable readers. For example, he has wisely included an analysis of the commercial infant foods available in Latin America. Furthermore, the chapter on tuberculosis is extensive, as it should be in a book destined to be used in countries with a high rate of tuberculosis. On the other hand, by the same criteria, the space devoted to typhoid fever, malaria and intestinal parasites is inadequate.

The personal touch with which the book is written makes it interesting reading. It is definitely Dr. Garrahan's book. He does not hesitate to give his own opinions even when they conflict with those generally held. It is reminiscent of Osler's approach in his "Principles and Practice of Medicine."

It is impossible in a review to praise adequately in detail the orderly and masterful treatment of specifically pediatric problems. This book must be read to be appreciated.

As a minor criticism of the publisher, the reviewer wishes to express his opinion that the excellent work of our Latin American colleagues deserve something better than paper covers.

Malaria im Kindesalter. By Albert Eckstein, M.D., Prof. Pediatrics and Director of the University Pediatric Clinic in Ankara, Turkey. Paper. Price, 14 Swiss francs. Pp. 119, with 48 illustrations. Basel, Switzerland and New York: S. Krager, Ltd., 1946.

The author draws on his experiences in Turkey with over 1,000 children with malaria. The volume is divided essentially into two parts. The first part is devoted to the prophylaxis of malaria and to the clinical manifestations of the disease in infancy and in childhood. The author emphasizes that from the points of view of incidence, clinical course and mortality rate, malaria in infants and children is not the same disease as malaria in adults. He also points out that the younger the infant with malaria, the more atypical is the course of the disease. The patterns of the temperature curves in the common forms of malaria, in malaria due to mixed infections and in cases in which several generations of parasites are sporulating at

different intervals are discussed at great length. Congenital malaria is considered in detail. The author stresses the criteria essential for the diagnosis of congenital malaria and points out the effectiveness of the placenta as a barrier to the passage of Plasmodia. The value of prophylaxis with quinacrine hydrochloride in pregnant mothers is considered. The cerebral, gastralgic, algid and bilious remittent forms of malaria are referred to as clinical manifestations of severe malaria rather than as partitcular disease entities. Undue emphasis is placed on nephritis as a complication.

In the second part the author discusses the manifestations of involvement of the central nervous system and treatment. He classifies these manifestations into seventeen separate groups and presents case reports illustrating each group. This classification complicates rather than simplifies the understanding of the cerebral form of malaria. The management of malaria with quinine, quinacrine hydrochloride and pamaquine naphtholate is presented. Much more emphasis might have been placed on this portion of the book, particularly in so far as it pertains to the treatment of severe forms of pernicious malaria. An interesting group of illustrations depicting, among other features, the amount of hepatic and splenic enlargement is included at the end of the book.

The Day Care of Little Children in a Big City. Dr. Leona Baumgartner, Cornelia Goldsmith and Yetta Bokhaut. Foreword by Howard W. Hopkirk. Price, 50 cents. Pp. 33, with 7 sketches and 1 table. New York: Child Welfare League of America, Inc., 1946.

In this booklet the Day Care Unit which provides group care for children under 6 years of age is described. The report is released by the Child Welfare League of America to depict the beneficial effect of a licensing service for nursery schools. "The Day Care Unit" whose activities are reported in the pamphlet was organized in 1943 and operated in the New York City Department of Health.

A survey was made of the existing facilities for day care of young children throughout the city. All types of facilities were encountered, ranging from convenient quarters with excellent programs to damp cellars encouraging neglect and even abuse of children.

Though the Municipal Sanitary Code has included laws that applied to centers giving group care to young children since 1895, little attention was given to factors other than fire protection, building standards and sanitation. The rapid increase in this type of institution during the early period of the war made inspection and supervision imperative.

For the successful operation of these numerous day nurseries minimum standards were set up covering not only the location of the center but the ratio of teachers to children. The Day Care Unit, with a competent staff, outlined the job to be done at the licenses centers, worked out plans with the nursery and with the aid of an educational consultant assisted the center in developing a sound program.

The pamphlet will serve as an excellent guide for municipalities interested in supervising child care centers.

Adolescent Sterility. M. F. Ashley Montagu. Price, $3.50. Pp. 157. Springfield, Ill.: Charles C Thomas, Publisher, 1946.

This short monograph is a comprehensive summary of the literature concerning adolescent sterility. From the assembled data the author concludes that the adolescent female is biologically immature, and developmentally unprepared for the processes of reproduction. The data with regard to the lower animals and

primates are well presented, and conclusive, and indicate without question that under normal circumstances the ability to conceive does not occur until a variable period after the appearance of overt evidence of maturity. In the human being the strongest evidence is of an anthropologic nature, and is compiled from the mass of literature dealing with races and tribes in which sexual intercourse at an early age is not only common, but acceptable. Extensive data concerning the age of the menarche in these people are presented; biologic statistics in these groups indicate that despite frequent intercourse the first pregnancy ordinarily does not occur for a significant period thereafter. In man, this period of absolute sterility following the menarche is said to be variable, the extremes being one month and seven years. On the basis of the case which the author presents, the overwhelming probability is that in the human being an adolescent sterility does exist. But the evidence will remain inferential until there is direct proof that ovulation does not normally occur during puberty or for a significant period thereafter, and that cyclic bleeding during this time is of the anovulatory type. Such evidence is not available.

The text is well written and readable. The format is excellent. The extensive bibliography is alphabetized by author at the end of the book. Complete references are also repeated in footnotes to the individual pages. The material which is presented should be of interest both to the pediatrician and to the gynecologist.

Monocular Vision Training. By Mildred Smith Evans. Price, $3. Pp. 93. Baltimore: The Williams & Wilkins Company, 1946.

Homework seeing exercise for the child's amblyopic eye is provided by the twenty-eight lessons of Mrs. Evans' manual. Designed as an adjunct to occlusion of the better vision eye, as employed by the ophthalmologist, each lesson includes a brief reading and writing exercise and a tracing of figures chosen for child interest. Type size diminishes from the twenty-four point of lesson one, requiring visual acuity of approximately 20/170, to the ten point of lesson twenty-eight, requiring visual acuity of approximately 20/70.

The Diagnosis and Treatment of Bronchial Asthma. Leslie N. Gay, M.D. Price, $5.00. Pp. 334. Baltimore: The Williams & Wilkins Company, 1946.

This monograph is a refreshing addition to the many books that have appeared recently on the subject of allergy.

Dr. Gay writes with a directness that is seldom found in medical literature. He is an author who says what he wants to say, and says it well. It is an opinionated book, and expresses the viewpoint of a physician who says what he believes in no indefinite terms. One might criticize this volume because it is not comprehensive either as a text or as a monograph. But whether or not one agrees with the author on all points, or whether there are on occasion glaring omissions and errors of fact, that detracts little from its value. The reader does get a clear picture in a field that is in sore need of clarification.

The reviewer believes that the author amply demonstrates for the benefit of the pediatrician the importance of treating bronchial asthma at its onset in childhood, and he shows how cause and effect become more and more obscured as one studies the disease in older persons.

The chapter on the pathology of asthma is the most comprehensive yet to appear in any book and will well repay careful reading. There is unmistakable evidence presented that a child can die in an attack of asthma, which emphasizes the need for careful treatment of this malady.

The chapter on the psychosomatic phase emphasizes properly the important role that the psyche plays in this disease. The author does stress, however, the importance of the detection of the allergenic factors even when the psyche appears to be the dominant factor, a viewpoint with which the reviewer heartily agrees.

This volume is the first that gives a description of the use of radium in the treatment of postpharyngeal adenopathy and its relation to allergy. It is worthy of the attention of all pediatricians.

Dr. Gay's book is wholeheartedly recommended to every physician who would like to understand the modern version of the diagnosis and treatment of asthma. The publishers are to be congratulated on an excellent job in the art of printing.

Précis clinique et opérative de chirurgie infantile. L. Ombrédanne. Fourth edition. Price, not given. Pp. 1015, with 1018 illustrations. Paris: Masson et Cie, 1944.

The fourth edition of this comprehensive work covering the surgery of childhood has, in addition to the text, a rather abbreviated index. It is based, as in previous editions, on the actual experience of the author and written in a terse, authoritative manner, on some subjects a little sketchy, on others fully explanatory and satisfying. The whole art and science of the surgery of childhood, fascinating as it is, is covered from the types and methods of anesthesia and when to use them to congenital and acquired deformities, traumas and diseases of all parts of the body, not only the limbs but internal organs as well. The descriptions of lesions, the discussions on embryologic development, informative paragraphs on pathogenesis and in many subjects detailed methods of clinical examination or operative procedure for correction and cure make the text valuable. The chapter on appendicitis alone is monographic. Withal there are dignified and enlightening diagrams and figures, many line drawings and some halftones scattered helpfully through the pages. The work of not only French surgeons and pathologists is mentioned but also there are many references to orthodox and worldwide accepted practices of English and American surgeons.

Unfortunately, there is no bibliographic reference for the research student, but the practitioner or pediatrician will find sufficient information on almost any subject he wishes to review, backed by Ombredanne's personal information or experience in its description.

The reviewer is amazed at the fine quality of the glossed paper employed, the excellence of the typography and the placing and size of illustrations, remembering that this edition must have been brought out under war conditions. The only criticism is the character of the binding—in loose paper which will not endure much handling.

Pediatricians will find this an up-to-date encyclopedic source of information in their work and may rely on the quality of the discussions and the saneness of advice for and description of treatment.

L'osteosynthese au clou. By R. Soeur. Price, not given. Pp. 130, with 116 illustrations. Paris: Masson et Cie, 1946.

The volume, although published in France where the paper shortage has been a serious one during the years of the war, is printed on an excellent grade of heavy paper and includes a total of 116 illustrations, the majority of which are roentgenographic prints.

Dr. Soeur describes and discusses methods of obtaining union of bones following fracture by means of nails or pins. In dealing with fractures of the shaft of the

femur he has used a long metal rod 18 to 35 cm. in length, which is introduced just above and medial to the tip of the greater trochanter, and varying in diameter depending on the size of the medullary cavity of the bone to be pinned. The technic of insertion, the choice of the size of the pin to be used and all details connected with this method have been carefully described. A similar but smaller metal pin has been used in the treatment of fractures of either the ulna or the radius or of both bones of the forearm when the fracture occurred in the middle third of the shafts. The author has used this method, beginning with the first case Sept. 17, 1943, with considerable success and complete satisfaction. The same principle has been applied to treatment of fractures of the shaft of the humerus, the clavicle and the tibia. For fractures of the neck of the femur, however, they have used a flanged nail similar to that described by Smith-Peterson.

Some of the roentgenograms they have included, although showing bony union, suggest death of the femoral head.

These authors have had a unique experience in the use of the materials described and their results have, for the most part, been good. Those surgeons who are trained in fracture technics will find this book of interest even though they may not care to depart from their own methods to try that which has been described herein.

The Master Hand: A Study of the Origin and Meaning of Right and Left Sidedness and Its Relation to Personality and Language. (Research Monographs No. 5, American Orthopsychiatric Association, Inc.) By Abram Blau, M.Sc., M.D., C.M. Price, $4.50. Pp. 206, with illustrations. New York: The American Orthopsychiatric Association, Inc., 1946.

In this monograph, the author, basing his conclusions on a critical analysis of available data, rejects the widely accepted hypothesis that handedness is an hereditary trait. Instead, he proposes that preferred laterality is a complicated, developmental trait with biologic endowment, learning experience, emotional reactions and social influence as prominent determining factors.

He explains the occurrence of left-handedness in 5 to 10 per cent of the population as due to: (1) an inherent deficiency, such as a physical defect in the right member enforcing the use of the left, or mental deficiency, (2) faulty education in the use of the hands and (3) emotional negativism.

Regarding the language centers, Blau proposes that cerebral dominance is determined by function. People are left-brained because they are right-handed, and the reverse is true of sinistrals.

Blau concludes that children should be encouraged in their early years to adopt right-handed habits. He believes that the alleged dangers of retraining are nonexistent. Left-handedness in a young child may be a danger signal pointing to emotional disturbances which require correction.

The book is written in clear, nontechnical language. It throws refreshing light on a field in which too much has been taken for granted.

The Compleat Pediatrician. W. C. Davison, M.D. Price, $3.75. Pp. 256. Durham, N. C.: Duke University Press, 1946.

This little volume, which has reached its fifth edition, has proved its value to many pediatricians and practitioners. It is not meant to replace the average textbook, but it does so in many ways. It is decidedly practical and has helped many a physician in his work with children. It has been brought thoroughly up to date and is a highly desirable book for a physician's library.

Directory of Pediatric Societies *

INTERNATIONAL

International Association of Preventive Pediatrics

President: Prof. S. Monrad, Dronning Louises Børnehospital, Copenhagen, Denmark.
Secretary: Dr. Daniel Oltramare, 15 Rue Lévrier, Geneva, Switzerland.

International Congress of Pediatrics

President: Dr. Henry F. Helmholz, Mayo Clinic, Rochester, Minn.
Secretary-General: Dr. L. Emmett Holt Jr., 477 First Ave., New York 16.
Canadian Committee:
Chairman: Dr. Alan Brown, Hospital for Sick Children, 67 College St., Toronto 2
Secretary: Dr. S. G. Ross, 1390 Sherbrooke St. W., Montreal.
Place: New York. Time: July 14-17, 1947.

International Congress for the Protection of Infancy

Secretary: Prof. G. B. Allaria, Corso Bramante 29, Torino 120, Italy.

Pan American Congress of Pediatrics

President: Dr. Felix Hurtado, Habana, Cuba.
Place: Mayflower Hotel, Washington, D. C. Time: July 9-12, 1947.

Save the Children International Union

President: Mrs. Gordon Morier.
Secretary: Dr. Georges Thélin, 43 Quai Wilson, Geneva, Switzerland.

FOREIGN

Argentine Pediatric Society of Buenos Aires

President: Dr. Martin Ramón Arana, 1809 Rodriguez Peña, Buenos Aires.
General Secretary: Dr. Alfredo Larguia, Cerrito 1179, Buenos Aires.

Associação Paulista de Medicina, Secção de Pediatrias

President: Dr. Vicente Lara.
First Secretary: Dr. Armando de Arruda Sampaio.
Second Secretary: Dr. Luiz Augusto Monteiro Toledo, Av. Brigadeiro Luiz Antonio 393, 1° Andar, São Paulo, Brazil.
Time: Twelfth of every month, 8:30 p. m.

British Paediatric Association

President: Prof. G. B. Fleming, 13 Lynedoch Crescent, Glasgow.
Joint Secretary: Prof. Alan Moncrieff, Hospital for Sick Children, Great Ormond St., London, W. 1.

Danish Pediatric Society

President: Prof. E. Lenstrup, Copenhagen.
Secretary: Dr. Gjørup, Dronning Louises Børnehospital, Copenhagen.

* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

Nederlandische Vereeniging voor Kindergeneeskunde

President: Dr. J. L. Keyzer, 114 St. Josephstr., Tilburg.
Secretary: Dr. H. Reerink, 2B Paul Krugerstr., Arnheim.
Place: Children's Hospital or Pediatric Clinic. Time: Three times a year.

Palestine Jewish Medical Association, Section of Physicians of Children's Diseases

President: Prof. L. F. Meyer, 29 Toelsohn St., Tel Aviv.
Secretary: Dr. A. Brünn, 9 Maazestre, Tel Aviv.

Royal Society of Medicine, Section for the Study of Diseases in Children

President: Dr. W. G. Wyllie, 33 Wimpole St., London W. 1, England.
Secretary: Dr. Philip Rainsford Evans, Keat's House, Guy's Hospital, London S. E. 1, England.
Place: 1 Wimpole St., London W. 1. Time: Fourth Friday of each month, 4:15 p. m.

Sociedad Boliviana de Pediatria

President: Dr. Ernesto Trigo Pizarro.
Secretary: Dr. Carlos Ferrufino, Casilla 272, La Paz, Bolivia.
Place: La Paz, Bolivia.

Sociedad Cubana de Pediatria

President: Dr. Teodosio Valledor, Habana.
Secretary: Dr. Carlos Hernandez Miyares, Hospital Nuestra Señora de las Mercedes L y 21, Apartado 2430, Habana.
Place: Cátedra de Clinica Infantil, Hospital Nuestra Señora de las Mercedes y Hospital Municipal de Infancia, Habana. Time: Last Wednesday of every month.

Sociedad Dominicana de Pediatria

President: Dr. Alberto Peguero, Ciudad Trujillo, R.D.
Secretary-Treasurer: Dr. Jaime Jorge, Ciudad Trujillo, R.D.
Place: Children's Ramfis Hospital. Time: 8 p. m., last Thursday of every month.

Sociedad Ecuadoriana de Pediatria

President: Dr. Francisco de Icaza Bustamente.
Secretary: Dr. M. I. Gómez Lince, P. O. Box 693, Guayaquil.

Sociedad Mexicana de Pediatria

President: Dr. Antonio Prado Vértiz, Edison 101, Mexico City, Mexico.
Secretary: Dr. Manuel Mendez, Hospital del Niño Mexico City, Mexico.

Sociedad de Pediatría de Córdoba

President: Dr. Juan Francisco Herrera, Córdoba, Argentina.
Secretary: Dr. Bernardo Serebrinsky, Dean Funes 2000, Esq. Ocaña (N.), Córdoba, Argentina.
Place: Comite pro Defenso del Niño, Dean Funes 2000, Córdoba, Argentina.
Time: Once a month.

Sociedad de Pediatria del Litoral

President: Dr. Jose E. Celoria, Hospital Centenario, Rosario, Argentina.
Secretary: Dr. Gloria Lovell, Hospital Centenario, Rosario, Argentina.

Sociedad de Pediatría de Santiago de Cuba

President: Dr. Antonio Béguez César, Sagarra 107, Santiago de Cuba.
Secretary: Dra. Susana Texdó Vaillant, Padre Pico 57, Santiago de Cuba.
Place: Colegio Médico. Time: Last Tuesday of every month.

Sociedad Venezolana de Puericultura y Pediatria

President: Dr. Pastor Oropeza, Caracas.
Secretary: Dr. Carlos E. Castillo, Hospital Municipal de Niños, Caracas.
Place: Hospital Municipal de Niños Jose Manuel de los Rios, Caracas.

Société de Pédiatrie de Paris

President: Dr. Leveuf, Paris, France.
Secretary: Dr. Jean Hallé, 10 bis Rue Pré aux Clercs, Paris, France.
Place: Hôpital des Enfants Maladies, 149 Rue de Sèvres. Time: 4:30 p. m., third Thursday of every month.

Swedish Medical Society, Section for Pediatrics and School Hygiene

President: Prof. Arvid Wallgren, 53 Strandvägen, Stockholm.
Secretary: Dr. Henning Magnusson, 58 Odengatan, Stockholm.
Place: Various clinics and hospitals in Stockholm and Uppsala. Time: Second Friday of each month (except summer).

Uruguayan Society of Pediatrics

President: Dr. Jose Bonaba, Montevideo.
Secretary: Dr. Héctor Fossatti, Durazno 1882, Montevideo.
Place: Club Medico del Uruguay, Avenida Agraciado 1464 (Piso 13), Montevideo.

NATIONAL

American Medical Association, Scientific Assembly, Section on Pediatrics

Chairman: Dr. Oscar Reiss, 2200 W. 3d St., Los Angeles.
Secretary: Dr. Margaret Mary Nicholson, 1801 Eye St. N. W., Washington, D. C.
Place: Chicago. Time: June 21-25, 1948.

American Academy of Pediatrics

President: Dr. Jay I. Durand, 515 Cobb Bldg., Seattle, Wash.
Secretary: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill.
Place: Dallas, Texas. Time: Dec. 8-11, 1947.
Regional Meetings:
Place: Buffalo, N. Y. Time: April 29-30 and May 1-2, 1948.
Place: Milwaukee, Wis. Time: June 28-30, 1948.
Place: Seattle, Wash. Time: Sept. 13-15, 1948.

American Hospital Association, Massachusetts Hospital Association

Chairman: Dr. Frank Wing, Boston.
Secretary: Dr. W. Franklin Wood, McLean Hospital, Waverly 79, Mass.

American Pediatric Society

President: Dr. Harold K. Faber, 2361 Clay St., San Francisco.
Secretary-Treasurer: Dr. Henry G. Poncher, 1819 W. Polk St., Chicago 12.

Canadian Society for the Study of Diseases of Children

President: Dr. Alan Ross, 1414 Drummund St., Montreal.
Secretary-Treasurer: Dr. R. L. Denton, 3534 Ontario Ave., Montreal.

Society for Pediatric Research

President: Dr. Donovan J. McCune, 3975 Broadway, New York.
Secretary: Dr. Robert Ward, Bellevue Hospital, New York 16.

SECTIONAL

Intermountain Pediatric Society

President: Dr. Wesley H. Anderson, 2404 Washington Blvd., Ogden, Utah.
Secretary-Treasurer: Dr. F. M. Kriete, State Capitol, Salt Lake City.
Place: Salt Lake City General Hospital. Time: First Thursday of each month, 8 p. m.

New England Pediatric Society

President: Dr. James Marvin Baty, 1101 Beacon St., Brookline, Mass.
Secretary-Treasurer: Dr. Charles D. May, 300 Longwood Ave., Boston.
Place: Boston Medical Library. Time: Three meetings a year, occurring from September to May.

North Pacific Pediatric Society

President: Dr. Percy Guy, 502–2d Ave., Seattle, Wash.
Secretary: Dr. Aldis B. Johnson, 515 Cobb Bldg., Seattle, Wash.

Northwestern Pediatric Society

President: Dr. George Kimmel, Redwing, Minn.
Secretary-Treasurer: Dr. Northrop Beach, 1009 Nicollet Ave., Minneapolis.
Place: Minneapolis, St. Paul, Duluth and Rochester. Time: January, April, July and October

Rocky Mountain Pediatric Society

President: Dr. Jackson L. Sadler, 109 W. Olive St., Ft. Collins, Colo.
Secretary: Dr. Edwin T. Williams, 1850 Gilpin St., Denver 6.

Southern Medical Association, Section of Pediatrics

Chairman: Dr. Stewart H. Welch, 117 S. 20th St., Birmingham 5, Ala.
Secretary: Dr. W. Ambrose McGee, 1601 Monument Ave., Richmond 20, Va.

STATE

Alabama Pediatric Society

President: Dr. Ruth Berrey, 2211 Highland Ave., Birmingham 5, Ala.
Secretary-Treasurer: Dr. W. A. Daniel Jr., 115 S. Union St., Montgomery 5, Ala.
Place: Birmingham. Time: September 1948.

Arizona Pediatric Society

President: Dr. W. P. Sherrill, 342 W. McDowell Rd., Phoenix.
Secretary: Dr. W. F. Schoffman, 926 E. McDowell Rd., Phoenix.
Place: Phoenix or Tucson. Time: At time of state meeting.

Arkansas State Pediatric Association

Chairman: Dr. C. B. Billingsley, 1425 N. 11th St., Fort Smith.
Secretary: Dr. R. E. Weddington, 1425 N. 11th St., Fort Smith.

California State Medical Society, Section on Pediatrics

Chairman: Dr. Charles W. Leach, 2000 Van Ness Ave., San Francisco 9.
Secretary: Dr. Chester I. Mead, 1930 Truxton Ave., Bakersfield.

Florida State Pediatric Society

President: Dr. James R. Boulware, Lakeland.
Secretary: Dr. Hugh A. Carithers, 2000 Park St., Jacksonville 4.
Place: Concurrent with state association convention and fall meeting.

Georgia Pediatric Society

President: Dr. Alton Johnson, 102 E. Central Ave., Valdosta.
Secretary-Treasurer: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.
Place: Atlanta. Time: At time of annual state meeting.

Hezekiah Beardsley Pediatric Club of Connecticut

President: Dr. F. M. Meyer, 144 Golden Hill St., Bridgeport, Conn.
Secretary: Dr. Herman Yannet, Southbury Training School, Southbury.

Illinois State Medical Society, Section on Pediatrics

Chairman: Dr. Gerard N. Krost, 2376 E. 71st St., Chicago.
Secretary: Dr. Frederick H. Maurer, 331 Fulton St., Peoria 2.

Indiana State Pediatric Society

President: Dr. K. T. Knode, 1105 E. Jefferson Bldg., South Bend.
Secretary-Treasurer: Dr. Matthew Winters, 621 Hume Mansur Bldg., Indianapolis.
Time: Two meetings a year.

Iowa Pediatric Society

President: Dr. Arnold M. Smythe, 406–6th Ave., Des Moines.
Secretary-Treasurer: Dr. James Dunn, 414 Blackhawk Hotel, Davenport.

Louisiana State Pediatric Society

President: Dr. R. V. Platou, 1430 Tulane Ave., New Orleans 13.
Secretary-Treasurer: Dr. Bertha Wexler, 3439 Prytania St., New Orleans 15.

Medical Society of State of New York, Section on Pediatrics

Chairman: Dr. Carl H. Laws, 12 Pierrepont St., Brooklyn, N. Y.
Secretary: Dr. George R. Murphy, 292 Madison Ave., New York.

Medical Society of the State of Pennsylvania, Pediatric Section

Chairman: Dr. Joseph A. Gilmartin, 3700–5th Ave., Pittsburgh 13.
Secretary: Dr. Carl C. Fischer, 100 W. Coulter St., Philadelphia 44.

Michigan State Medical Society, Pediatric Section

Chairman: Dr. Donald J. Barnes, 3001 W. Grand Blvd., Detroit, Mich.
Secretary: Dr. Mark F. Osterlin, Central Michigan Children's Clinic, Traverse City.

Mississippi State Pediatric Society

President: Dr. Harvey F. Garrison Jr., 315 E. Capitol Pl., Jackson.
Secretary: Dr. Guy Verner, 126 N. Congress St., Jackson.

Nebraska Pediatric Society

President: Dr. Paul N. Morrow, 1614 Medical Arts Bldg., Omaha 2.
Secretary-Treasurer: Dr. Michael Crofoot, 1407 Medical Arts Bldg., Omaha 2.
Place: As announced by committee. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

New Mexico State Pediatric Society

President: Dr. M. K. Wylder, 221 W. Central Ave., Albuquerque.
Secretary-Treasurer: Dr. Ly Werner, 221 W. Central Ave., Albuquerque.

North Carolina Pediatric Society

President: Dr. Charles R. Bugg, Professional Bldg., Raleigh.
Secretary: Dr. Charles F. Williams, 817 Hillsboro St., Raleigh.

Northern California Pediatric Society

President: Dr. Edith M. Meyers, 431–30th St., Oakland.
Secretary: Dr. A. L. Gleason, 411–29th St., Oakland 9.
Place: San Francisco. Time: Second Thursday of February, April, September and November.

Oklahoma State Pediatric Society

President: Dr. J. B. Snow, 625 N. W. 10th St., Oklahoma City.
Secretary: Dr. Bertha Levy, 1200 N. Walker St., Oklahoma City.
Place: With Oklahoma State Medical Association. Time: Annual Meeting.

South Carolina Pediatric Society

President: Dr. George D. Johnson, Spartanburg.
Secretary-Treasurer: Dr. B. O. Ravenel, Roper Hospital, Charleston.

Tennessee Pediatric Society

President: Dr. Harold J. Starr, 803 Medical Arts Bldg., Chattanooga 3.
Secretary-Treasurer: Dr. W. O. Vaughan, 2105 Hayes St., Nashville 5.
Time: Second Monday in April.

Texas Pediatric Society

President: Dr. Max Woodward, 202 N. Travis St., Sherman.
Secretary-Treasurer: Dr. John E. Ashby, 3610 Fairmount Ave., Dallas 4.

Virginia Pediatric Society

President: Dr. Emily Gardner, 1100 W. Franklin St., Richmond 20.
Secretary: Dr. Louise Galvin, 214 S. Boulevard, Richmond 21.

West Virginia State Medical Society, Section on Pediatrics

President: Dr. Jack Basman, 1021 Quarrier St., Charleston.
Secretary: Dr. Harry E. Baldock, Medical Arts Bldg., Charleston.

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Academy of Medicine of Cleveland, Pediatric Section

Chairman: Dr. J. I. Hartman, 10515 Carnegie Ave., Cleveland.
Secretary: Dr. Alexander N. Freed, 2012 W. 25th St., Cleveland.
Place: Cleveland Medical Library Bldg. Time: 8:15 p. m., October, December, February and April.

Academy of Medicine, Toronto, Section of Pediatrics

President: Dr. J. H. Ebbs, 13 Queen's Park, Toronto, Canada.
Secretary: Dr. J. F. McCreary, 170 St. George St., Toronto, Canada.
Place: Academy of Medicine. Time: 8:30 p. m., third Thursday of each month.

Baltimore City Medical Society, Pediatric Section

Chairman: Dr. Charles O'Donovan Jr., 5 E. Read St., Baltimore.
Secretary: Dr. T. Campbell Goodwin, 16 E. Biddle St., Baltimore.

Bronx Pediatric Society

President: Dr. Harry S. Pizer, 1726 Davidson Ave., New York.
Secretary: Dr. Nathan M. Greenstein, 1488 Metropolitan Ave., New York.
Place: Morrisania City Hospital. Time: 8:30 p. m., second Wednesday of each month, except June, July, August and September.

Brooklyn Academy of Pediatrics

President: Dr. George E. Brockway Jr., 176 Fenimore St., Brooklyn.
Secretary: Dr. Bernard Benjamin, 845 Park Pl., Brooklyn 16.
Place: Granada Hotel. Time: 8:45 p. m., fourth Wednesday of February, March, April, October and November.

Buffalo Pediatric Society

President: Dr. Douglas P. Arnold, 159 Bidwell Parkway, Buffalo, N. Y.
Secretary: Dr. Richard A. Downey, 786 Forest Ave., Buffalo 9, N. Y.
Place: Children's Hospital, 219 Bryant St. Time: 8:30 p. m., first Monday of each month from September to June.

Central New York Pediatric Club

President: Dr. Arthur W. Benson, 2 St. Paul St., Troy.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Places: Various cities in New York. Time: Third Tuesday of April and October.

Chicago Pediatric Society

President: Dr. H. William Elghammer, 2371 E. 71st St., Chicago.
Secretary: Dr. Alvah L. Newcomb, 723 Elm St., Winnetka, Ill.
Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May inclusive.

Cincinnati Pediatric Society

President: Dr. Leo S. Friedman, 666 Rockdale Ave., Cincinnati 29.
Secretary: Dr. George Renner, 3144 Jefferson Ave., Cincinnati.
Place: Children's Hospital, Elland Ave., Cincinnati. Time: On call.

Dallas Pediatric Society

President: Dr. Shirley Hodges, 2703 Oak Lawn Ave., Dallas, Texas.
Secretary-Treasurer: Frances M. Love, 4585 Belfort, Dallas 4.
Place: Children's Medical Center. Time: 1 p. m., third Saturday and 8:30 p. m. the first Thursday of each month.

Detroit Pediatric Society

President: Dr. Otto Grob, 651 Fisher Bldg., Detroit 2, Mich.
Secretary: Dr. Harold B. Rothbart, 773 Fisher Bldg., Detroit 2, Mich.
Place: Variable. Time: Third Wednesday of each month.

Houston Pediatric Society

President: Dr. George Salmon, 1220 Bartlett St., Houston, Texas.
Secretary: Dr. Betty Moody, 526 Richmond Rd., Houston, Texas.
Place: River Oaks Country Club. Time: 7:30 p. m., last Tuesday of each month.

Kansas City (Missouri) Pediatric Society

President: Dr. Harry M. Gilkey, 1624 Professional Bldg., Kansas City.
Secretary: Dr. Leland Speer, 1022 Parkway, Kansas City.
Place: Kansas City General Hospital. Time: On call.

Knoxville-Oak Ridge Pediatric Society

President: Dr. Henry S. Christian, 205 Medical Arts Bldg., Knoxville, Tenn.
Secretary: Dr. John Eggleston, Oak Ridge Hospital, Oak Ridge, Tenn.

Los Angeles County Medical Association, Pediatric Section

President: Dr. Elena Boder, 1830½ Lucille Ave., Los Angeles 26.
Secretary-Treasurer: Dr. Robert Simonds, 267 S. Beverly Dr., Beverly Hills, Calif.
Place: Los Angeles County Medical Association Bldg., 1925 Wilshire Blvd. Time: Second Monday of February, April, June, October and December.

Medical Society of the County of Kings and the Academy of Medicine of Brooklyn, Pediatric Section

President: Dr. Henry Rascoff, 895 Eastern Parkway, Brooklyn.
Secretary: Dr. Harold Levy, 750 St. Marks Ave., Brooklyn.
Place: 1313 Bedford Ave., Brooklyn. Time: 9:00 p. m., fourth Monday of each month.

Medical Society of the County of Queens, Inc., Section on Pediatrics

Chairman: Dr. Meyeron Coe, 217-02-91st Ave., Queens Village, N. Y.
Secretary-Treasurer: Dr. Louis Appel, 143-42 Cherry Ave., Flushing, N. Y.
Place: Queens County Medical Bldg., Forest Hills, N. Y. Time: Third Monday of October, January, March and May.

Medical Society of the District of Columbia, Section on Pediatrics

President: Dr. John Washington, 2203 Wyoming Ave., Washington, D. C.
Secretary-Treasurer: Dr. George Maksim, 1418 Good Hope Rd. S.E., Washington. D. C.
Place: Medical Society Bldg., 1718 M St. N. W. Time: 8 p. m., third Thursday of October, January, March and May.

Memphis Pediatric Society

President: Dr. Kinsey M. Buck, 1193 Madison Ave., Memphis, Tenn.
Secretary-Treasurer: Dr. Barton Etter, 1024 Madison Ave., Memphis, Tenn.

Milwaukee Pediatric Society

President: Dr. Roy Greenthal, 425 E. Wisconsin Ave., Milwaukee 2, Wis.
Secretary-Treasurer: Dr. Katharine Baird, 1411 Wauwatosa Ave., Wauwatosa 13, Wis.
Place: Milwaukee Children's Hospital. Time: Second Wednesday in February, April, June, October and December.

New York Academy of Medicine, Section of Pediatrics

Chairman: Dr. Robert O. Du Bois, 122 E. 76th St., New York.
Secretary: Dr. Harold W. Dargeon, 1095 Park Ave., New York.
Place: New York Academy of Medicine, 2 E. 103d St. Time: Second Thursday of each month from November to May, inclusive, 8:30 p. m.

Oklahoma City Pediatric Society

President: Dr. J. B. Snow, 625½ N. W. 10th St., Oklahoma City.
Secretary: Dr. Bertha Levy, 1200 N. Walker St., Oklahoma City.
Place: Oklahoma Club. Time: Third Thursday of each month.

Philadelphia Pediatric Society

President: Dr. Arthur M. Dannenburg, 235 S. 15th St., Philadelphia 2.
Secretary: Dr. D. Stewart Polk, Rosemont, Pa.
Place: College of Physicians, 19 S. 22d St. Time: 8:30 p. m., second Tuesday from October to May, inclusive.

Pittsburgh Pediatric Society

President: Dr. Elwood Stitzel, 403 Central Trust Bldg., Altoona, Pa.
Secretary-Treasurer: Dr. C. J. Stoecklein, Medical Arts Bldg., Pittsburgh 13.
Place: Pittsburgh Academy of Medicine. Time: Second Friday in October, December, February and April.

Richmond Pediatric Society

President: Dr. Edwin L. Kendig Jr., 828 W. Franklin St., Richmond 20, Va.
Secretary-Treasurer: Dr. Thomas S. Chalkley, 1200 E. Broad St., Richmond, Va.
Place: Medical College Hospital. Time: 8 p. m., third Thursday of each month, except June, July and August.

Rochester Pediatric Society

President: Dr. Jerome Glaser, 300 S. Goodman St., Rochester 7, N. Y.
Secretary-Treasurer: Dr. Daniel B. Peeler, 1162 Lake Ave., Rochester 13, N. Y.
Place: Rochester Academy of Medicine or arrangement by program committee.
Time: Third Friday of each month from October to May.

St. Louis Pediatric Society

President: Dr. Joseph C. Jaudon, 337 N. Euclid Ave., St. Louis.
Secretary-Treasurer: Dr. Gilbert B. Forbes, 500 S. Kingshighway, St. Louis 10.
Time: Second Thursday of each month from October to May, inclusive.

San Antonio Pediatric Society

President: Dr. Sidney R. Kaliski, 518 Moore Bldg., San Antonio 5.
Secretary-Treasurer: Dr. Edith M. Bonnet, 228 Medical Arts Bldg., San Antonio 5.
Place: Variable. Time: 7:30 p. m., first Tuesday of every month.

Seattle Pediatric Society

President: Dr. Norman W. Murphy, 1300 Madison St., Seattle 4.
Secretary: Dr. David M. Harris, 630 Medical Arts Bldg., Seattle 1.
Place: College Club. Time: Third Friday of each month from September to June at 6:30 p. m.

Southwestern Pediatric Society

President: Dr. Donald C. Shelby, 416 N. Bedford Dr., Beverly Hills, Calif.
Secretary: Dr. Harry F. Dietrich, 416 N. Bedford Dr., Beverly Hills, Calif.
Place: University Club of Los Angeles. Time: 6:30 p. m., first Wednesday in January, March, May, September and November.

University of Michigan Pediatric and Infectious Disease Society

President: Dr. Park Bradshaw, Muskegon, Mich.
Secretary: Dr. Harry A. Towsley, 1313 E. Ann St., Ann Arbor, Mich.

Westchester County Medical Society, Pediatrics Section (New York)

President: Dr. John B. Ahouse, 27 Ludlow St., Yonkers, N. Y.
Secretary-Treasurer: Dr. Elvira Ostlund, 64 Highland Rd., Rye, N. Y.
Place: Hospitals of Westchester County. Time: Third Thursday in November, January, March and May.